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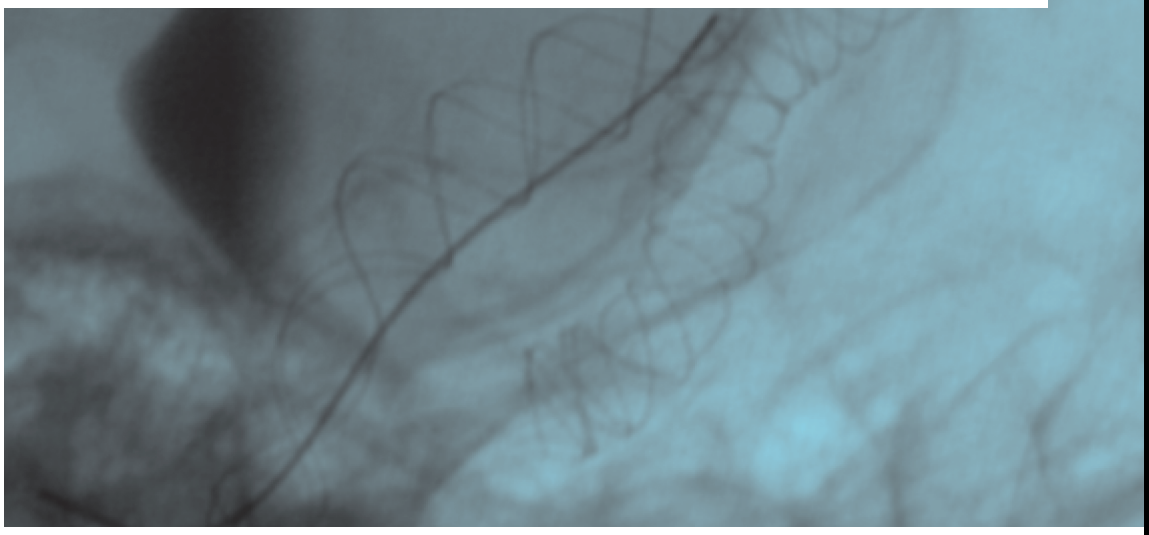
Olli Tähtinen

Stent-assisted Endovascular Therapy of Complex Intracranial Aneurysms



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UNIVERSITY OF
EASTERN FINLAND

OLLI TÄHTINEN

Stent-assisted Endovascular Therapy of Complex Intracranial Aneurysms

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ABSTRACT

Endosaccular coil embolization was introduced in 1991 as an alternative, minimally invasive approach in the treatment of cerebral aneurysms. The embolization system consists of a microcatheter which is transarterially delivered into the aneurysm and a very soft and flexible platinum coil which is detached from the delivery wire into the aneurysm sac, thus promoting aneurysm thrombosis and exclusion of the aneurysm from the circulation. Coil embolization of very wide-necked or otherwise complex cerebral aneurysms is, however, often technically challenging since the coils may protrude from the aneurysm into the parent artery. Intracranial stents, initially launched in 2002, were developed to provide additional support and remodeling of the aneurysm neck, and the concept of parent artery reconstruction was further advanced with flow-diverting stents introduced in 2008.

The development of intracranial stents has revolutionized the endovascular management of complex intracranial aneurysms and the proportion of aneurysms allocated to endovascular therapy ranges from 10 % to 90 %. Many previously untreatable cerebral aneurysms (i.e. fusiform or dissecting aneurysms or aneurysms with a wide-necked profile) are now within the scope of endovascular treatment, but many limitations remain. Our knowledge of the effectivity and safety of advanced endovascular techniques is often insufficient and the treatment options are still far from comprehensive. The aim of this thesis was to evaluate the feasibility and safety of stent-assisted embolization in the treatment of recurrent or residual cerebral aneurysms, stent-assisted embolization of acutely ruptured wide necked cerebral aneurysms, and the applicability of flow-diverting stents in the endovascular therapy of complex intracranial aneurysms.

This study is based on the patients with intracranial aneurysms treated with either stent-assisted embolization or with a flow-diverting stent in Kuopio University Hospital, Tampere University Hospital, and Turku University Hospital during the study period from February 2003 to June 2011. In the case of recurrent aneurysms, the initial coil embolization or surgical ligation of the aneurysm had been performed between October 1997 and July 2008. In addition to evaluating the technical success of the procedure, angiographic and clinical outcomes were retrospectively assessed. Special attention was focused on the procedure-related complications and in finding factors associated with poor clinical outcome.

Stent-assisted coil embolization is a feasible endovascular treatment method for ruptured wide-necked intracranial aneurysms which are difficult to treat surgically or with balloon-assisted embolization also during acute SAH. Stent-assisted embolization is beneficial also for the treatment of wide-necked recurrent or residual intracranial aneurysms, although stability and permanent occlusion of the aneurysm is unlikely if the aneurysm exceeds 20 mm in diameter, the recurrent diameter of the aneurysm exceeds 10 mm, or if mass effect is present with the recurrent aneurysm. Flow-diverting stents, on the other hand, offer another valuable tool in the endovascular treatment of complex cerebral aneurysms. Many previously untreatable aneurysms may be successfully treated with a flow-diverting stent,

but the associated risk of thromboembolic events is justifiable only if conventional endovascular or surgical treatment options are not applicable.

National Library of Medicine Classification:
Medical Subject Headings: Endovascular Procedures; Intracranial Aneurysm; Stents; Subarachnoid Hemorrhage; Aneurysm, Ruptured

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TIIVISTELMÄ

Ensimmäiset aivovaltimoaneurysmien embolisaatiohoidot tehtiin 1990-luvun alussa viemällä aneurysman sisälle mikrokatetrin kautta platinakoileja, jotka verenvirtauksen uudelleenohjautumisen ja hyytymisjärjestelmän aktivoitumisen kautta sulkevat aneurysman verenkierrosta. Hyvin leveäkantaisten tai muutoin kompleksien aivovaltimoaneurysmien suonensisäinen embolisaatiohoito on kuitenkin usein haastavaa, sillä koilit saattavat pyrkiä työntymään ulos aneurysmasäkistä. Tämän ehkäisemiseksi kehitetyt verkkoproteesit eli stentit tulivat markkinoille vuonna 2002 ja vuonna 2008 esiteltiin ensimmäiset verenvirtauksen uudelleenohjautumiseen perustuvat ns. flow diverting -stentit.

Stenttien nopea kehittyminen on mullistanut aivovaltimoaneurysmien suonensisäisen hoidon ja keskusten hoitokäytännöistä riippuen 10–90 % kaikista aivovaltimoaneurysmista voidaan nykyisin hoitaa suonensisäisesti. Hoitomenetelmissä on kuitenkin edelleen useita rajoitteita ja tiedot uusien suonensisäisten hoitomenetelmien vaikuttavuudesta ja turvallisuudesta ovat lisäksi puutteellisia. Tämän tutkimuksen tarkoitus on selvittää stenttiavusteisen embolisaatiohoiton vaikuttavuutta ja turvallisuutta uusiutuneiden ja jäännösaneurysmien sekä puhjenneiden leveäkantaisten aivovaltimoaneurysmien hoidossa sekä toisaalta uusien verenvirtauksen uudelleenohjautumiseen perustuvien stenttien (ns. flow diverting -stenttien) käytettävyyttä kompleksien aivovaltimoaneurysmien hoidossa.

Tutkimusaineisto koostuu Kuopion yliopistollisessa sairaalassa, Tampereen yliopistollisessa sairaalassa sekä Turun yliopistollisessa sairaalassa helmikuun 2003 sekä kesäkuun 2011 välissä stenttiavusteisesti hoidetuista aivovaltimoaneurysmapotilaista, joista seulottiin kunkin osatyön mukainen tutkimuskohortti retrospektiivisessä asetelmassa. Uusiutuneiden aivovaltimoaneurysmien osalta aneurysmien primaarihoito oli toteutettu lokakuun 1997 ja heinäkuun 2008 välissä. Toimenpiteiden teknisen onnistumisen lisäksi tutkimuksessa arvioitiin hoitotuloksen pysyvyyttä sekä potilaiden kliinistä tilaa seuranta-ajan puitteissa. Erityistä huomiota kiinnitettiin hoidon komplikaatioiden raportointiin ja komplikaatioille sekä hoidon epäonnistumiseen altistavien tekijöiden löytämiseen.

Stenttiavusteinen embolisaatio on käyttökelpoinen hoitomenetelmä myös sellaisten puhjenneiden leveäkantaisten aivovaltimoaneurysmien hoidossa, jotka eivät sovellu kirurgiseen tai palloavusteiseen embolisaatiohoitoon. Stenttiavusteinen embolisaatio soveltuu myös uusiutuneiden sekä jäännösaneurysmien hoitoon joskin hyvän ja pysyvän hoitotuloksen saavuttaminen on epätodennäköistä mikäli aneurysma on läpimitaltaan yli 20 mm, aneurysman rekanalisoitunut osa on läpimitaltaan yli 10 mm tai aneurysmaan liittyy massavaikutusta ympäröiviin rakenteisiin. Tutkimuksessa todettiin myös, että verenvirtauksen uudelleenohjautumiseen perustuvat flow diverting -stentit mahdollistavat useiden vaikeahoitoisten aivovaltimoaneurysmien hoidon, mutta toimenpiteeseen liittyvät, pääosin verihyytymien muodostumiseen liittyvät riskit ovat perusteltuja vain mikäli perinteiset suonensisäiset tai kirurgiset hoitomenetelmät eivät ole sovellettavissa aneurysman hoitamiseksi.

Luokitus:
Yleinen Suomalainen asiasanasto: aneurysma; kallonsisäinen aneurysma; stentit; lukinkalvonalainen verenvuoto

Primum non nocere

An ancient axiom of the medical profession

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Kuopio, November 2014

Olli Tähtinen

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List of the original publications

This dissertation is based on the following original publications:

I Tahtinen OI, Vanninen RL, Manninen HI, Rautio R, Haapanen A, Niskakangas T, Rinne J, Keski-Nisula L. Wide-necked intracranial aneurysms: treatment with stent-assisted coil embolization during acute (<72 hours) subarachnoid hemorrhage--experience in 61 consecutive patients. *Radiology 253(1):199-208, 2009.*

II Tahtinen OI, Manninen HI, Vanninen RL, Rautio R, Haapanen A, Seppanen J, Niskakangas T, Rinne J, Keski-Nisula L. Stent-assisted embolization of recurrent or residual intracranial aneurysms. *Neuroradiology 55(10):1221-1231, 2013.*

III Tahtinen OI, Manninen HI, Vanninen RL, Seppanen J, Niskakangas T, Rinne J, Keski-Nisula L. The silk flow-diverting stent in the endovascular treatment of complex intracranial aneurysms: technical aspects and midterm results in 24 consecutive patients. *Neurosurgery 70(3):617-623, 2012.*

Contents

Abbreviations

ACA	Anterior cerebral artery
AComA	Anterior communicating artery
ACT	Activated clotting time
aSAH	Aneurysmal subarachnoid hemorrhage
BA	Basilar artery
CCA	Common carotid artery
CE-MRA	Contrast-enhanced magnetic resonance angiography
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	Computed tomography angiography
CTP	Computed tomography perfusion
DCI	Delayed cerebral ischemia
DSA	Digital subtraction angiography
FLAIR	Fluid attenuated inversion recovery
GCS	Glasgow coma scale
GDC	Guglielmi detachable coil
GOS	Glasgow outcome scale
H&H	Hunt and Hess scale
ICA	Internal carotid artery
ICG-VA	Indocyanide green videoangiography
ICH	Intracerebral hematoma
ISAT	International Subarachnoid Aneurysm Trial
ISUIA	International Study of Unruptured Intracranial Aneurysms
IVH	Intraventricular hematoma
MCA	Middle cerebral artery
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
OR	Odds ratio
PCA	Posterior cerebral artery
PComA	Posterior communicating artery
PED	Pipeline Embolization Device
PTA	Percutaneous transluminal angioplasty
RR	Relative risk (i.e. risk ratio)
SAH	Subarachnoid hemorrhage
TOF-MRA	Time-of-flight magnetic resonance angiography
VA	Vertebral artery
WEB	Woven EndoBridge Cerebral Aneurysm Embolization Device

1 Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating condition with 30-day mortality of up to 45 %, almost half of the survivors left disabled even with modern methods of diagnosis and treatment.[1-6] Poor outcomes related to aSAH could theoretically be avoided by preventing the aneurysm rupture, which is the primary goal of aneurysm treatment. All of the treatment options are, however, associated with procedural risks and only a minority of the asymptomatic aneurysms will eventually rupture and cause aSAH. The risks associated with potential treatment methods should therefore be carefully evaluated and weighed against the estimated risk of aneurysm rupture prior to initiating aneurysm therapy. Endovascular therapy of cerebral aneurysms is firmly established, but the morphology of the aneurysm (i.e. large size and/or fusiform or wide-necked profile) may preclude conventional coil embolization of the aneurysm. Microsurgical treatment, either by aneurysm clipping or by bypass surgery possibly combined with parent vessel occlusion is often the primary treatment method of these complex cerebral aneurysms, but since the surgical treatment is also occasionally met with difficulties, a need for advanced endovascular techniques is established.[7-13]

Intracranial stents have several theoretical advantages in the treatment of cerebral aneurysms. In addition to disturbing the inflow jet to the aneurysm sac and thus promoting aneurysm thrombosis, the presence of the stent reduces the risk of coil protrusion and provides a physical matrix for possible endothelial growth across the aneurysm neck. There are, however, also many limitations in stent-assisted coiling. The reconstruction of very wide-necked or fusiform aneurysms with coils may be difficult and even accessing the aneurysm sac after stenting may prove challenging, the dual antiplatelet therapy necessitated by the stent may be problematic especially in the setting of acute subarachnoid hemorrhage, and even when adequate occlusion has been initially achieved with stent-assisted embolization, aneurysms remain prone to coil compaction and recanalization.

Flow-diverting stents, on the other hand offer fascinating opportunities for the treatment of segmentally diseased vessels and complex cerebral aneurysms.[14-19] The concept of flow redirection and curative vessel reconstruction represents a paradigm shift in the treatment philosophy for endovascular aneurysm therapy. However, many uncertainties remain with this relatively new form of aneurysm treatment, including i.a. the lack of long-term knowledge of the risk of arterial stenosis after stent deployment, the fate of perforating vessels crossed by the device, the duration of post-procedural antiplatelet medical therapy, and optimal patient selection.

The rapidly developing and constantly changing field of endovascular aneurysm therapy offers an intriguing and fascinating field to investigate, the importance of which is accentuated by the knowledge that the incidence of aSAH in Finland is among the highest in the world, affecting approximately 1200 patients each year, often in the working age.[20-22] The treatment of intracranial aneurysms is challenging and advanced surgical and endovascular treatment methods are often complementary, emphasizing the role of multidisciplinary team approach in the treatment of intracranial aneurysms.

2 *Review of the literature*

2.1 INTRACRANIAL ANEURYSMS

An aneurysm is literally an abnormal focal dilatation of an artery (derived from the Greek word *aneurýnein*, to dilate). Intracranial aneurysms are usually classified by their general phenotypic appearance into saccular and non-saccular aneurysms. While vast majority of cerebral aneurysms are saccular, pouch-like dilatations encountered predominantly in arterial bifurcations, other types of focal arterial dilatations (i.e. arterial dissecations, pseudoaneurysms, or fusiform arterial dilatations) are also often collectively called aneurysms, although they may have very little in common with saccular aneurysms. The terminology used to describe non-saccular aneurysms is also somewhat heterogenous. Some definitions are descriptive and based on the aneurysm morphology (i.e. fusiform, dolichoectatic), while others are related to the etiology of the aneurysm (i.e. dissecting or mycotic). Regardless of their etiology aneurysms form a focal discontinuity and a weak spot in the vessel wall, predisposing to aneurysm rupture, the most frequent cause of non-traumatic subarachnoid hemorrhage (SAH).

While aneurysmal SAH is the most common presentation of intracranial aneurysm rupture, the hemorrhage from an intracranial aneurysm may not be confined to the subarachnoid space but can also rupture into the brain parenchyma, the ventricular system, or rarely the subdural space.[23,24] Unruptured cerebral aneurysms are usually asymptomatic, but they may cause symptoms (i.e. cranial nerve palsies or brain-stem compression symptoms) by exerting a mass effect to adjacent structures.[25]

2.1.1 Epidemiology and risk factors

The epidemiology of cerebral aneurysms differs to some extent from the epidemiology of aneurysmal SAH since most of the intracranial aneurysms never rupture and the annual risk of aneurysm rupture may be as low as 0.05 % in some aneurysms.[26] The estimated prevalence of cerebral aneurysms varies considerably according to study design, study population, and aneurysm characteristics. Combining the data of autopsy and radiological studies, the prevalence of intracranial aneurysms is around 2 % (0.2–9 %) for adults without specific risk factors.[24,26,27]

In a comprehensive systematic review of the literature, the prevalence of cerebral aneurysms was shown to be higher in patients with autosomal dominant polycystic kidney disease (relative risk [RR], 4.4), a familial predisposition (RR, 4.0), or systemic atherosclerotic vascular disease (RR, 2.3).[26] The prevalence of intracranial aneurysms is ca. 12 % in patients affected with polycystic kidney disease, 7 % in patients with fibromuscular dysplasia, and 5 % in patients with syndromic diseases of connective tissues (notably Ehlers-Danlos type IV).[28] In addition to various connective tissue diseases, systemic inflammatory diseases (e.g. Takayasu arteritis, systemic lupus erythematosus, giant cell arteritis) may produce modifications of the arterial wall predisposing to aneurysm formation.[5] Female gender seems to increase the risk for aneurysm formation, but does not affect the risk of aneurysm rupture to the same extent.[29] It has also been suggested that smoking, in addition to increasing the risk of aneurysm rupture, is also a risk factor for aneurysm formation.[29] Epidemiology and risk factors of aneurysmal SAH are discussed in paragraph 2.2.1.

2.1.2 Familial predisposition

Familial intracranial aneurysms not associated with any of the known hereditable connective tissue disorders account for approximately 10 % (7–20 %) of aneurysmal SAH, and first-degree relatives of subjects with ruptured intracranial aneurysms have three- to sevenfold higher risk of aSAH than the general population.[5,30-33] Familial intracranial aneurysms are reportedly more commonly multiple and rupture at a slightly smaller size and on average five years earlier than sporadic intracranial aneurysms.[28] Aneurysms of the middle cerebral artery are over-represented and those of the anterior cerebral artery and posterior communicating artery are underrepresented among the familial intracranial aneurysms when compared to sporadic intracranial aneurysms.[28,34,35] The rupture rate of unruptured cerebral aneurysms in the Familial Intracranial Aneurysm study cohort (1.2 % per year) was approximately 17 times higher than the rupture rate for subjects with an unruptured cerebral aneurysm in the International Study of Unruptured Aneurysm Study (0.069 % per year) with a matched distribution of aneurysm size and location.[32,36] Aneurysm formation is a dynamic process and *de novo* aneurysms may form also after negative screening of the cerebral vasculature. In individuals with a family history of aSAH, a long-term serial screening has been advocated since the yield of screening may be substantial even after more than 10 years of follow-up and two initial negative screens.[37]

A number of genetic alterations have been associated with saccular aneurysms, most of which are moderators of cell cycle progression. Genome-wide genotyping of Finnish and Dutch cohorts and replication studies in a Japanese cohort identified common single nucleotide polymorphism on chromosomes 2q, 8q, and 9p that show significant association with intracranial aneurysms (OR 1.24–1.36).[33] In a Finnish cohort, genome-wide linkage analysis showed linkage to 19q13 and Xp22, both of which were replicated in Japan.[38-40] Many of the identified genes affect the proliferation and senescence of cell populations that are primarily responsible for vascular formation and repair.

2.1.3 Saccular intracranial aneurysms

Intracranial aneurysms are classified, according to their morphology, into saccular and non-saccular aneurysms. Saccular aneurysms account for more than 85 % of all intracranial aneurysms (Fig. 1).[24,41] In general, saccular aneurysms develop when the cerebral artery wall becomes too weak to resist the hemodynamic pressure in the vessel, preferentially at the outer curvatures, bifurcations, or branching points of the brain vessels where hemodynamic stresses are maximal. Saccular aneurysms are extremely rare in pediatric population and are therefore almost exclusively acquired, not congenital lesions and develop with increasing age.[42,43] Almost 90 % of saccular aneurysms occur on the anterior (i.e. carotid) circulation, most of them being situated on the circle of Willis.[5,24] Although extensively studied, the definitive etiology of these focal outpouchings of the vessel wall remains largely unknown.

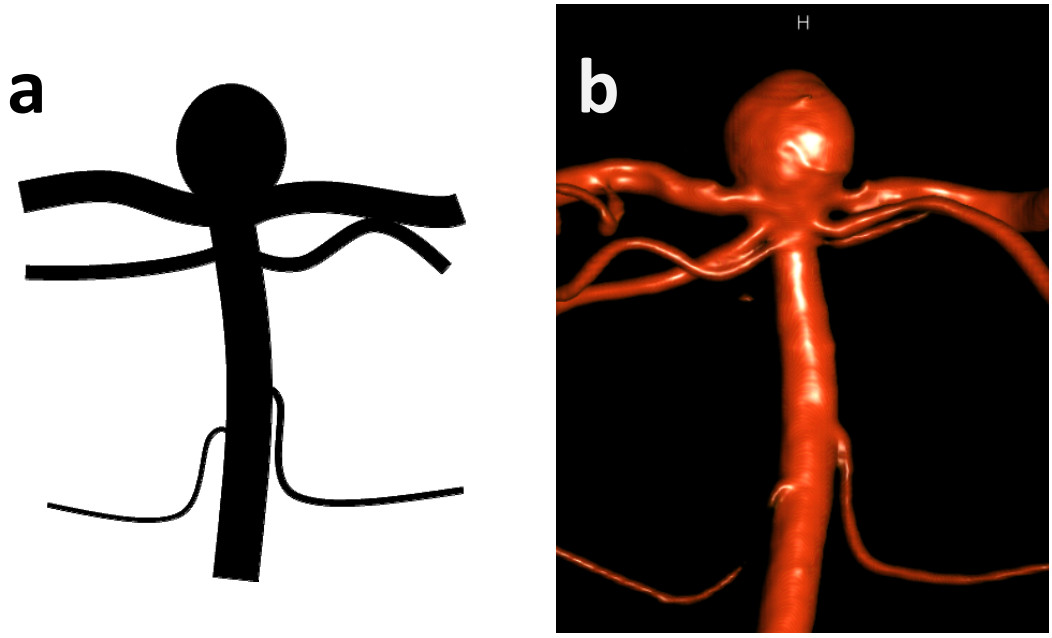

Figure 1. A schematic presentation (a) and a three-dimensional digital subtraction angiograph (DSA) reformation (b) of a typical saccular basilar tip aneurysm.

Theoretically, all factors either deteriorating the tensile strength of the vessel wall or increasing the hemodynamic shear stress may predispose to aneurysm formation. In animal models, cerebral aneurysms have been induced by a combination of hypertension and disruption of collagen synthesis.[44,45] Association between apoptosis of medial smooth muscle cells and formation of saccular cerebral aneurysms was demonstrated in an animal model with induced cerebral aneurysms.[46] In addition, degenerative changes in the internal elastic lamina related to early aneurysmal changes in another animal model, suggesting that aneurysmal alterations progress from the luminal towards the abluminal side of arterial wall if synthesis on the abluminal side is imbalanced with the catabolism on the luminal side of the vessel wall.[47] Inflammation of the cerebral artery wall may also decrease the tensile strength thus predisposing to aneurysm formation. In immunohistochemical studies, however, the degree of inflammatory cell infiltration has been shown to be higher in ruptured than unruptured cerebral aneurysms, and inflammation seems to be a reaction to the ongoing degenerative processes in the aneurysm wall rather than the cause of the aneurysm.[48] Consequently, the pathobiology behind aneurysm formation may be different from that of aneurysm rupture (see paragraph 2.2.2).

Saccular aneurysms vary in size from very small (1–2 mm in diameter) to very large (several sentimeters in diameter). Intracranial aneurysms are classically categorized by their largest diameter into small (less than 10 mm), large (10 mm to 25 mm), and giant (over 25 mm) aneurysms, although other categorizations are also frequently used (e.g. small <7 mm; medium 7–12 mm; large 13–24; giant ≥25 mm). Some saccular aneurysms remain stable over time, whereas some saccular aneurysms grow, sometimes regardless of any treatment attempts. Approximately 20–33 % of cerebral aneurysm patients have multiple aneurysms, about a third of these patients have three or more aneurysms, and less than 1 % of the aneurysm patients have six or more aneurysms.[49-51]

2.1.4 Fusiform aneurysms

In contrast to saccular aneurysms, fusiform aneurysms often involve long, nonbranching vessel segments and the demarcation between the normal and diseased vessel is less distinct in fusiform than in saccular aneurysms (Fig. 2). Often the fusiform aneurysm

consists of most, if not all, of the parent artery circumference. Fusiform aneurysms can be either atherosclerotic or nonatherosclerotic, of which atherosclerotic fusiform aneurysms are substantially more common. Although a strong association between fusiform arterial dilatation and atherosclerosis has been reported, surgical and pathological studies of symptomatic fusiform aneurysms have shown contradictory results and atherosclerosis seems to be only one of the mechanisms in the pathogenesis of these lesions.[52-55] Non-atherosclerotic fusiform aneurysms are seen in younger patients and are often associated with an inherited vasculopathy or immune deficiency.[56]

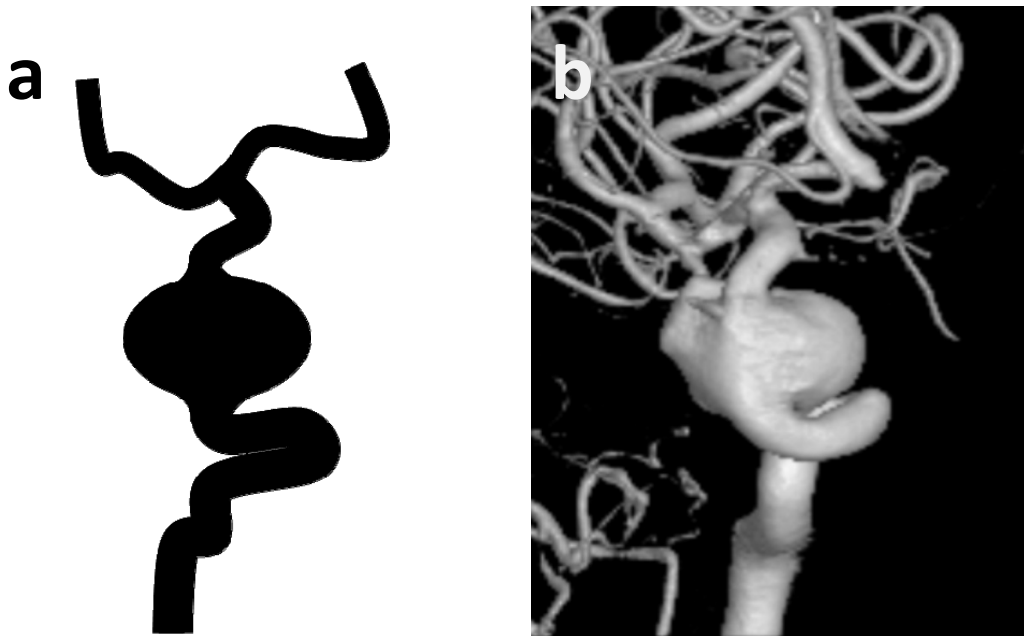

Figure 2. A schematic presentation *(a)* and a three-dimensional DSA reformation *(b)* of a fusiform internal carotid artery aneurysm.

The term "dolichoectasia" (dilative arteriopathy) is used to refer to fusiform elongation of vessels without focal fusiform or saccular dilatations, alluding to their elongated and distended shape (derived from the Greek words *dolichos*, long or elongated, and *éktasi*, extension). It has been estimated that approximately one patient in eight who has intracranial vascular imaging has some increase in the length and diameter of intracranial arteries, most of which may be considered as physiological elongation and widening of the arteries, forming a certain overlap in the terminology between fusiform aneurysms, dolichoectasia, and normal elongation of the intracranial arteries.[57,58]

If symptomatic at all, fusiform aneurysms may present with ischemic or compression symptoms. Since dilatative arteriopathy preferentially involves the intracranial vertebral and basilar arteries, the tortuous elongated arteries may generate pressure and distortion of brain structures especially in the medulla and pons as well as irritative symptoms caused by the stretching of cranial nerves (i.e. trigeminal pain, tinnitus, etc.)[58] Dilatative arteriopathy may also cause ischemic strokes by distorting the orifices of arterial branches leading to decreased blood flow especially in penetrating branches of the large arteries, causing, for example, basilar artery branch territory infarcts in the pons.[59] Rupture of fusiform aneurysms is unusual and most of these aneurysms have a benign prognosis.[53,60]

2.1.5 Blister-like aneurysms

Blister-like or blood blister-like aneurysms are small, thin-walled, and broad-based bulges frequently located at the non-branching, proximal part of the basal arteries of the anterior circulation (Fig. 3). Medial and anterior curvature of the terminal ICA segment not related to the choroideal or posterior communicating artery branches is the usual location for blister-like aneurysms, although other locations (e.g. basilar and anterior communicating arteries) are also possible. In pathological studies, focal arterial wall defects covered almost exclusively with fibrous tissue are demonstrated and blister-like aneurysms may originate from a focal dissection of the vessel wall.[61,62] Blister-like aneurysms are rare, accounting for about 1 % of all intracranial aneurysms. In addition, it often remains unclear whether all radiological bulges of ICA are true blister-like aneurysms, especially in non-ruptured cases. Blister-like aneurysms are, however, known to be associated with much higher bleeding rates than saccular cerebral aneurysms and their fragile structure may also predispose to intraoperative rupture of the aneurysm.[62-65]

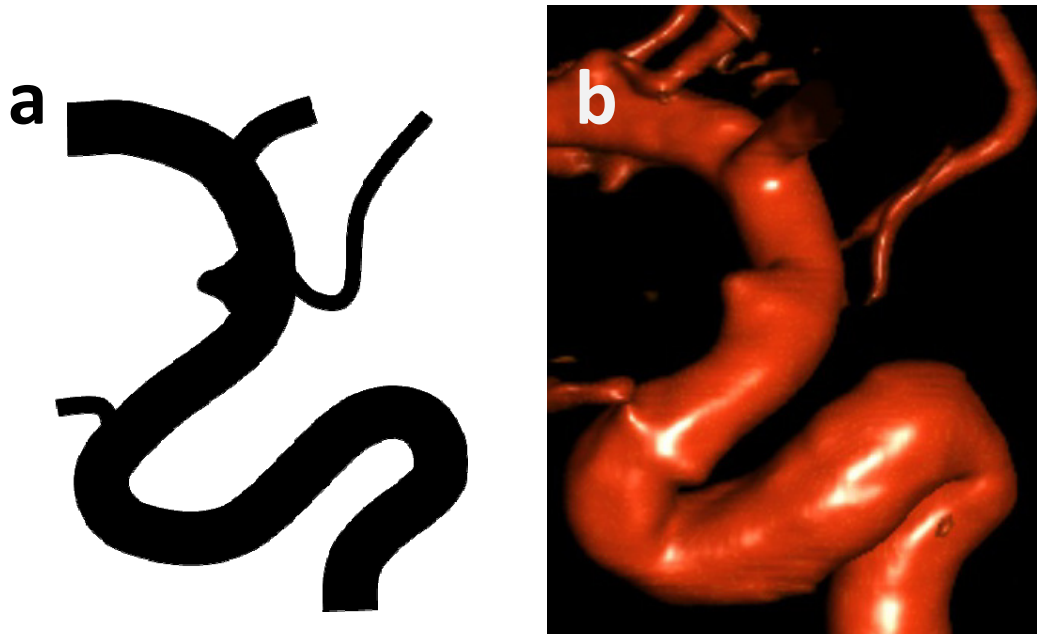

Figure 3. A schematic presentation *(a)* and a three-dimensional DSA reformation *(b)* of a blister-like aneurysm of the internal carotid artery.

2.1.6 Dissecting aneurysms and pseudoaneurysms (i.e. false aneurysms)

Both dissecting aneurysms and pseudoaneurysms are characterized by a focal disruption of the vessel wall and are histologically not considered true aneurysms (Fig. 4). While dissecting aneurysms are contained by a thinned, often discontinuous adventitia, pseudoaneurysms are contained only by surrounding paravascular hematoma.[66] Dissecting aneurysms and pseudoaneurysms may however be difficult to differentiate and they often result from a specific inciting event (e.g. infection, neoplastic process, vasculitis, rupture of true cerebral aneurysm or arteriovenous malformation, or [iatrogenic] trauma).[67-69]

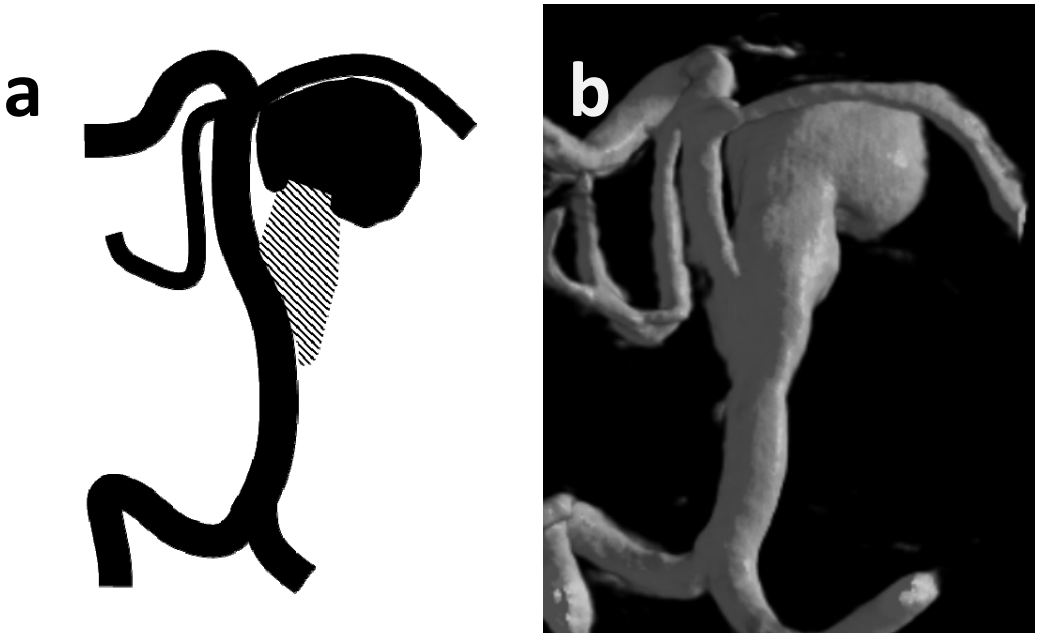

Figure 4. A schematic presentation *(a)* and a three-dimensional DSA reformation *(b)* of a dissecting basilar artery sidewall aneurysm.

The primary mechanism by which cerebral dissecting aneurysms are created is by the disruption of internal elastic lamina. The majority of these aneurysms have one entrance into the pseudolumen while some dissecting aneurysms have a clinically more stable configuration with both an entrance and exit.[68] Intracranial artery dissection may also result in luminal stenosis, thromboembolism, and cerebral ischemia. Prognosis depends on clinical presentation, and presentation with SAH has a worse prognosis than presentation with cerebral ischemia.[69] While both pseudoaneurysms and dissecting aneurysms are rare, the fragile structure of these lesions makes them susceptible to repeated hemorrhage and especially in pseudoaneurysms presenting with SAH, the rate of mortality can be high (14–63 %).[67-70] In a series of 12 rare peripheral posterior inferior cerebellar artery aneurysms, most were secondary to arterial dissection.[71] The aneurysms were unstable with a high risk of rebleeding and a high mortality if not treated without delay, and endovascular treatment was effective in preventing rehemorrhage.

2.1.7 Traumatic aneurysms

Traumatic cerebral aneurysms are complications of closed and penetrating head injuries or may result also from surgical or endovascular procedures. They constitute less than 1 % of all intracranial aneurysms. Traumatic aneurysms may be caused either by direct injury of the arterial wall or by acceleration/induced shear, and it may be unclear whether they should be classified as (dissecting) aneurysms contained by surrounding hematoma and thinned tunica adventitia or pseudoaneurysms. Pathological findings, however frequently seem to reveal disruption of the three vascular layers fulfilling the definition of a pseudoaneurysm.[66]

More than 50 % of traumatic cerebral aneurysms are reportedly associated with a skull fracture.[72] Traumatic aneurysms typically arise near the skull base from the petrous or cavernous segments of ICA, from dural vessels, and especially in pediatric population also from pericallosal artery and its branches. In children, traumatic aneurysms observed after a severe head trauma are slightly overrepresented accounting for 14 % to 39 % of all aneurysms, partially due to the rareness of saccular aneurysms in this population.[5,66]

2.1.8 Infectious aneurysms

Infectious aneurysms are rare, accounting for 0.7 % to 6 % of all cerebral aneurysms, and can be caused by a myriad of pathogens.[73,74] While often called mycotic aneurysms, the vast majority of infectious aneurysms result from bacterial infections. Bacterial aneurysms are typically found in patients with endocarditis and usually result from embolization of fragments of vegetations from an infected cardiac valve, and bacterial endocarditis carries an estimated risk of 3–10 % of aneurysm formation. Less commonly, infectious aneurysms result from direct extension of intracranial bacterial infections (i.e. meningitis, orbital cellulitis), often in immunocompromised patients.[74,75]

Due to the presence of infection and destruction of the walls of the vessels, infectious aneurysms are typically thin-walled and friable, often with a wide or absent neck. Infectious aneurysms are associated with a higher risk of rupture and fatal hemorrhage when compared to other aneurysms. Even small infectious aneurysms can rupture and bleed fatally, and mortality rates of up to 80 % have been reported following infectious aneurysm rupture.[76] In other, more recent series consisting of unruptured aneurysms, however, much lower mortality rates (12–32 %) have been reported.[73-75,77]

2.1.9 Pediatric intracranial aneurysms

Although a genetic component to aneurysm development and rupture have been demonstrated, very few saccular aneurysms are congenital (i.e. present at birth). In a systematic review of the literature, Garg et al. stated that pediatric aneurysms are uncommon as compared to aneurysms in adult patients, and there are many differences in the aneurysm etiology, location and morphological characteristics, and clinical presentation and outcome in pediatric and adult intracranial aneurysms.[78] While pediatric aneurysms are heterogenous and can occur as a result of various etiologies, there is a high incidence of post-traumatic and infectious aneurysms in children.[41]

Intracranial aneurysms cause the majority of spontaneous SAH in children and account for 10–15 % of hemorrhagic strokes in patients less than 20 years of age.[79] Since pediatric aneurysms are frequently relatively large, develop a more complex shape, and have a predilection for the posterior circulation, seizures and cranial nerve involvement are seen more often as the presenting symptoms in children. In a series of 74 pediatric intracranial aneurysms in 62 children, the most common presenting feature was headache (82 %; 51 of 62), followed by loss of consciousness (27 %; 17 of 62), limb weakness (23 %; 14 of 62) and seizures (21 %; 13 of 62).[78] In a Finnish, population-based study of 114 pediatric patients with 130 aneurysms treated between 1937 and 2009, symptomatic *de novo* aneurysm formation was observed in six patients after a median of 25 years (range 11–37 years), and even a lifelong follow-up at five- to 10-year intervals was proposed for pediatric patients with ruptured intracranial aneurysms.[80]

2.2 ANEURYSMAL SUBARACHNOID HEMORRHAGE

Intracranial aneurysm rupture accounts for approximately 85 % of cases of nontraumatic SAH.[24,41] Aneurysmal SAH is a devastating disease with overall 30-day case fatality rate of about 45 %. In addition, almost half of survivors are left disabled. Although SAH comprises only 3 % (1–7 %) of all strokes, SAH accounts for more than one-quarter of potential life years lost through stroke.[41] Due to the poor clinical outcome and relatively young age of the affected patients, the loss of productive life years from aSAH is comparable to that of ischemic cerebral stroke, the most common stroke subtype.[41,81,82]

2.2.1 Incidence and risk factors of aSAH

The incidence of aneurysmal SAH is in Finland among the highest in the world. Whereas the age-adjusted incidence of aneurysmal SAH is approximately 11 per 100 000 per year in

most Western populations, it is about twice as much in Finland and in Japan.[20-22] In a multinational epidemiological study, the age-adjusted annual SAH attack rates varied 10-fold among the 11 populations studied, from 2.0 per 100 000 per year in China-Beijing to 22.5 per 100 000 per year in Finland.[20]

2.2.1.1 Patient-dependent risk factors of aSAH

Statistically significant modifiable risk factors of aneurysmal SAH in longitudinal and case-control studies were current smoking (RR 2.2), hypertension (RR 2.5), and excessive alcohol intake (RR 2.1).[81,83] In addition, cocaine use has also been identified as a modifiable risk factor of aneurysmal SAH.[2] Female gender and younger age at the beginning of the follow-up may increase the risk of aneurysmal SAH, but the reported confidence intervals are relatively wide and the risk of rupture of a cerebral aneurysm seems to depend more on the characteristics of the aneurysm than on those of the patient.[26,29,81,83,84]

Aneurysmal SAH is a strong risk factor for subsequent rerupture of the aneurysm. If a ruptured cerebral aneurysm is left unsecured, the risk of rerupture is estimated to be ca. 20 % in the first two weeks after subarachnoid hemorrhage.[85,86] Furthermore, prior history of aneurysmal SAH is a strong risk factor for aneurysm rupture also for unruptured cerebral aneurysms. In the International Study of Unruptured Intracranial Aneurysms (ISUIA), patients with unruptured intracranial aneurysms and prior subarachnoid hemorrhage had approximately 11 times higher rupture rates than patients with unruptured intracranial aneurysms and no prior history of SAH.[87]

2.2.1.2 Aneurysm related risk factors of aSAH

Aneurysm size (especially in patients who have not had previous SAH) and location have a significant role in determining the risk of future rupture of a cerebral aneurysm.[3,88] In the ISUIA study, subjects with unruptured intracranial aneurysms of less than 7 mm in diameter and without a previous history of SAH, the rupture rate was very low (ca. 0.1 % annually). In giant aneurysms with a diameter of ≥25 mm the 5-year cumulative rupture rates were, on the other hand, as high as 50 % if the aneurysm was located in the posterior circulation or in the posterior communicating artery (PComA) (Table 1).[3,36] The ISUIA study has, however, been criticised for multiple methodological inadequacies biased in favour of a benign natural history of small aneurysms.[89,90] In addition, saccular aneurysms do not enlarge at a constant rate. The growth of saccular aneurysms is highly variable and unpredictable and although large aneurysm size is a known risk factor for aneurysm rupture and ruptured aneurysms are usually larger than unruptured aneurysms, the risk of rupture is not insignificant in small aneurysms and should not be predicted on aneurysm size alone.[91,92] In a recent prospective Finnish cohort study of 118 patients with unruptured intracranial aneurysms diagnosed between 1956 and 1978 and followed up until death or SAH, the lifelong risk of aneurysm rupture was 29 % (34 of 118 patients).[93] In small (<7 mm) unruptured aneurysms, the lifelong risk of aneurysm rupture was 25 % (24 of 96 patients).

Aneurysm location also predicted aneurysm rupture in the ISUIA study: the relative risk of rupture was 2.3 if the aneurysm was in the tip of basilar artery, 2.1 if the aneurysm was located in the PComA, and 0.15 in the cavernous carotid artery, with internal carotid artery as the reference group. Although anterior communicating artery (AComA) aneurysms form 30 % to 35 % of ruptured aneurysm series, only 10 % to 15 % of more than 5500 patients had AComA aneurysms in the ISUIA study, implying that AComA aneurysms are prone to rupture early and do not tend to stabilize for a long time (i.e. be included in longitudinal studies involving unruptured cerebral aneurysms).[36] Analogous results were shown in another cohort study with a very long follow-up data (median 21.0 years), in which AComA aneurysms showed a significant association with the risk of rupture while aneurysm location in the PComA and internal carotid bifurcation did not reach statistical significance.[84]

Table 1. 5-year cumulative rupture rates for patients without a history of subarachnoid hemorrhage (Wiebers et al. 2003).

Aneurysm location	Aneurysm size			
	<7mm	7–12mm	13–24mm	≥25mm
Cavernous carotid artery	0	0	3.0 %	6.4 %
ICA, AComA, ACA, MCA	0	2.6 %	14.5 %	40 %
Post., PComA	2.5 %	14.5 %	18.4 %	50 %

In addition to aneurysm size and location, numerous aneurysm related risk factors (i.e. aneurysm shape, various size and shape ratios, flow angles, and contact between the aneurysm wall and surrounding anatomic structures) have also been identified.[94-98] Studies on these morphological and geometric characteristics have, however, somewhat conflicting results, possibly due to variation in imaging techniques and other methodological differences.[99] There is marked variation in the definition of aneurysm shape parameters, and there is a lack of consistency even in the definition of aneurysm size, which is the most ubiquitous parameter used in rupture risk assessment.[95] Aneurysms with a daughter sac, however, were associated with a higher rate of rupture than aneurysms with a smooth wall also in a large prospective cohort of 5720 patients.[88]

2.2.2 Aneurysm rupture as a biochemical process

Considering the thinning and histopathological changes observed in the aneurysm wall and the increase in the hemodynamic load resulting from uneven wall shear stress and pressure distribution in the aneurysm sac, it may be more difficult to rationalize why an aneurysm *does not* inevitably rupture, rather than why it occasionally does. Nevertheless, the rupture of an aneurysm is a complex biochemical process, which is not yet fully understood. Cerebral aneurysms induced in animal models (e.g. by ligation of the common carotid artery combined with experimental hypertension and β-aminopropionitrile feeding) rarely rupture, suggesting that the pathobiology leading to formation of an intracranial aneurysm is not entirely identical to that leading to the rupture of an existing aneurysm.[44,45,48]

Rupture-prone aneurysm wall is thought to develop when the equilibrium between vascular proliferation and degradation becomes disturbed. Loss of mural cells (e.g. due to excessive oxidative stress) along with the loss of functioning endothelium (e.g. due to aberrant flow conditions in the aneurysm lumen) have been presented as the key events which lead to intrinsic activation of cell death in the aneurysm wall and shift the balance towards aneurysm wall degeneration.[100] Since mural cells seem to be essential for maintaining aneurysm wall homeostasis, loss of mural cells leads to aneurysm recanalization and increased inflammatory responces resulting in aneurysm wall degeneration, aneurysm growth, and eventual aneurysm rupture.[101] Whether an intracranial aneurysm will eventually rupture or not seems to depend on both the hemodynamic shear stress and the biochemical responses leading to remodeling and restructuring of the aneurysm wall.[48]

2.2.3 Clinical presentation, diagnostic studies, and imaging of aSAH

The clinical presentation of aneurysmal SAH is often quite distinctive with a severe headache of sudden onset, which may be associated with additional signs and symptoms including nausea and/or vomiting, stiff neck, loss of consciousness, and focal neurological

deficits including cranial nerve palsies. An estimated 10 percent of the patients die before reaching medical attention, and many others present in coma or with severe neurologic compromise.[25] However, because the type of headache from SAH is variable and nearly half of all patients with SAH have normal results on neurological examination as well as normal vital signs at initial presentation, misdiagnosis or delayed diagnosis of aSAH is relatively common with documented misdiagnosis rates of approximately 12 %.[24,102-104] Misdiagnosis is reportedly associated with a nearly four-fold higher likelihood of death or disability at one year in patients with minimal or no neurological deficit at the initial visit.[102] Since the most common diagnostic error is failure to obtain a nonenhanced cranial CT scan, a low threshold for CT scanning of patients with mild symptoms is advocated.[4,102]

Clinical grading scales such as the Hunt and Hess scale (Table 2) are often used to objectively describe the neurologic condition on admission and are also considered relatively good predictors of clinical outcome.[25,105]

Table 2. Hunt & Hess Grading Scale for subarachnoid hemorrhage (Hunt, Hess 1968).

Grade	Clinical presentation
I	Asymptomatic or mild headache
II	Moderate to severe headache; nuchal rigidity, and no neurologic deficit other than cranial-nerve palsy
III	Drowsiness, confusion, or mild focal deficit
IV	Stupor, moderate-to-severe hemiparesis, and possibly, early decerebrate rigidity and vegetatite disturbances
V	Coma, decerebrate rigidity, and moribund appearance

Non-enhanced CT of the head is the initial diagnostic test of choice if SAH is clinically suspected. Lumbar puncture is traditionally recommended if the initial computed tomogram yields negative results, with bloody cerebrospinal fluid that fails to clear with continued egress or the presence of xanthocromia (yellowish discoloration of the CSF representing bilirubin from the breakdown of hemoglobin) raising a suspicion of SAH. In a large prospective multicenter study, modern computed tomography, when carried out within six hours of headache onset and interpreted by a qualified radiologist, was extremely sensitive and specific (sensitivity 100 % [CI 97.0 % to 100.0 %]; specificity 100 % [99.5 % to 100 %]; negative predictive value 100 % [99.5 % to 100 %]; and positive predictive value 100 % [96.9 % to 100 %]) in identifying subarachnoid hemorrhage.[104]

In another study of 134 patients admitted with acute SAH and imaged with a 16-slice CT, the sensitivity of CT was 97.8 % (95 % CI 93.1–99.4 %) and none of the patients with negative CT had a lesion requiring intervention (Gee et al. 2012). In this setting, CT can be considered a "rule out" test for SAH and the need for lumbar puncture is questionable. If the CT was performed after six hours from the time of headache onset, however, the sensitivity dropped to 85.7 % (CI 78.3 % to 90.9 %), and when performed within six days after the onset of the symptoms, MRI (combination of fluid attenuated inversion recovery [FLAIR] and susceptibility weighted imaging [SWI]) yielded a distinctly higher detection rate for SAH than CT.[104,106]

If SAH is detected in non-enhanced CT, CT angiography (CTA) is performed to detect possible underlying vascular pathology. CTA is a highly sensitive and specific non-invasive imaging method for diagnosis and evaluation of intracranial aneurysms, and CTA has been proposed as an alternative to DSA as a first-line imaging technique in patients with SAH.[107] However, in a prospective study of 200 SAH patients, the sensitivity of CTA, when compared to that of DSA, was 95.2 % in detecting cerebral aneurysms.[108] The specificity of CTA was 97.2 %, positive predictive value 98.1 %, and negative predictive value 93.2 %.

Due to the suboptimal sensitivity and negative predictive values of CTA, continued use of DSA was recommended in patients with a negative CTA after acute SAH except for patients with classic perimesencephalic blood distribution.

2.2.4 Complications of aSAH

2.2.4.1 Vasospasm and delayed cerebral ischemia

Delayed cerebral ischemia (DCI), defined either on the basis of cerebral infarction and functional disability or as a new onset of clinical deterioration not explained by other causes, is considered the most significant cause of morbidity and mortality in patients who survive the acute phase of SAH. DCI is used to complement older clinicoradiographic terminology (angiographic vasospasm and symptomatic vasospasm) as the pathogenesis of DCI in not fully attributable to large-vessel vasospasm. Angiographic vasospasm occurs in up to 70 % of SAH patients, but the relationship between angiographic spasm and clinical symptoms can be inconsistent.[109,110] Other factors important in the pathophysiology and prognosis of DCI include disturbed cerebral autoregulation, global ischemia, disruption of the blood-brain barrier, microthrombosis, and activation of apoptotic and inflammatory pathways.[111-113]

Cerebral vasospasm or rather delayed cerebral ischemia usually develops approximately one week after the hemorrhage and the condition worsens the prognosis of the hemorrhage significantly with poor outcomes occurring in up to 30 % of the affected patients despite aggressive therapy.[114,115] In a Japanese study of 370 patients with ruptured aneurysms, the most important risk factors for cerebral vasospasm were SAH grade III-IV, left ventricular hypertrophy, cigarette smoking, and hypertension.[116] Both DSA and CTA imaging are applicable in the evaluation of large-vessel vasospasm, but the hemodynamic alterations in cerebral perfusion leading to parenchymal ischemia can be assessed only by CT or MR imaging. Specifically CT perfusion (CTP) allows for rapid and noninvasive assessment of cerebral perfusion and is useful in the detection of DCI. In a systematic review, patients with aneurysmal SAH with perfusion deficits in CTP were approximately 23-fold more likely to experience DCI compared with SAH patients with normal CTP results.[115]

Different combinations of hemodilution, hypervolemia, and hypertension have been used to increase cerebral blood flow in delayed cerebral ischemia. When all three components are used, the treatment combination is called triple-H therapy.[117] In a systematic review on the effects of triple-H therapy, induced hypertension seemed to be the most promising in increasing cerebral blood flow (CBF). No good evidence was, however, found that CBF improves due to the intervention.[118,119] Avoidance of hypotension, hyponatremia, hypovolemia, hyperglycemia, and hyperthermia has been recommended to prevent DCI in SAH patients.[120] Intra-arterial papaverine, nimodipine, and balloon angioplasty have also been utilized in the treatment of vasospasm, often when triple-H therapy is ineffective or cannot be used due to risk of hemodynamic complications (e.g. heart failure or pulmonary edema).[121] Both intra-arterial vasodilation administration and PTA have been shown to successfully reduce vasospasm and neurological deficits, although complications with both therapies (i.e. vessel rupture during PTA and intracranial hypertension and possible neurotoxicity associated with intra-arterial medical therapy) have also been reported.[113,122-125]

2.2.4.2 Hydrocephalus and other complications of aSAH

The range of the reported risk of hydrocephalus after aneurysmal SAH is wide, varying from 6 % to 67 % depending i.a. on the definition of hydcephalus, inclusion criteria, and timing of neuro-imaging studies.[1,126,127] In a large study of 3521 SAH patients, the most important variables associated with clinically symptomatic hydrocephalus were the findings of hydrocephalus and intraventricular hemorrhage on admission CT, impaired level of consciousness at admission, preexisting and postoperative hypertension, increasing

age, and posterior circulation aneurysm site.[128] Other factors, such as hyponatremia and the use of antifibrinolytic drugs preoperatively contributed also to the development of acute hydrocephalus and the development of hydrocephalus after SAH was concluded to be multifactorial. While external ventricular drainage is required in approximately half of the patients with acute hydrocephalus, permanent CSF diversion is required in only 10–20 % of the cases. Risk factors for shunt-dependent hydrocephalus were the presence of intra-ventricular hemorrhage, lower mean score of Glasgow Coma Scale, and complications with post-operative intra-cerebral hemorrhage.[127]

Benign cardiac abnormalities (e.g. ST segment depression, prolonged QT segments, and tall peaked T-waves) are common in the first 48 hours after SAH, and cardiac enzymes are often mildly elevated.[6] Only in rare cases the neurogenic cardiopulmonary abnormalities are severe (e.g. fall in cardiac output; development of pulmonary edema).[129] Fever, anemia, hyperglycemia, hyponatremia, hypertension, and pneumonia have also been reported as a complication of SAH, and hyponatremia may also be an independent risk factor for poor outcome.[4] Although a large number of seizure-like episodes have been associated with aneurysmal rupture, the risk and implications of seizures associated with SAH are not well defined and it is unclear whether all these episodes are epileptic in origin. Nonrandomized studies of craniotomy patients have indicated a benefit of prophylactic anticonvulsants, but the number of patients has been relatively small in these studies and the routine use of prophylactic anticonvulsants during the perioperative period is still ambiguous.[4,130-132]

2.2.5 Non-aneurysmal SAH

Approximately 15 % of patients with non-traumatic SAH have normal cerebral angiograms.[133] The definitive cause of angiogram-negative SAH has not been established although various pathogenetic causes (i.e. abnormalities in the venous structures, capillary or perforating artery ruptures, intramural hematomas, and low-flow vascular malformations) have been suggested.[134-137] The clinical outcome in patients with nonaneurysmal SAH is substantially better than in patients with aneurysmal SAH, although two distinct subsets of patients with angiogram-negative SAH should be recognized, namely perimesencephalic and non-perimesencephalic non-aneurysmal SAH.[133] Especially patients with a perimesencephalic pattern of hemorrhage have an excellent prognosis with a clinically good outcome in 89–100 %.[138-141] In addition, the long-term mortality in patients with perimesencephalic SAH does not differ from that observed in the general population.[138]

2.3 CLINICAL OUTCOME AFTER aSAH

Aneurysmal SAH is often a devastating event. Approximately 10 % of patients with aSAH die prior to reaching medical attention, 25 % die within 24 hours of aSAH onset, and about 45 % die within 30 days. Only a third of the patients will have a good outcome after treatment.[1-6] There are, however relatively wide variations in case fatality rates reported between different studies and slightly declining mortality rates during the past several decades have also been suggested, presumably explained by the improved management of patients with aSAH.[20,142,143]

The clinical outcome after aSAH is often assessed with Glasgow Outcome Scale (GOS), which allows standardized descriptions of the objective degree of recovery (Table 3).[144]

Table 3. Glasgow Outcome Scale (GOS) (Jennett, Bond 1975).

Grade	Clinical outcome
1	Death
2	Persistent vegetative state
3	Severe disability (conscious, but totally dependent on others)
4	Moderate disability (neurological deficit or intellectual impairment, but independent life)
5	Good recovery (independent life, no or minimal neurological deficit)

In addition, modified Rankin Scale (mRS) is often used to assess the degree of disability or dependence in the daily activities after aSAH (Table 4).[145] An additional grade (6; death) is often added to mRS classification.

Table 4. Modified Rankin Scale (mRS) (Farrell et al. 1991).

Grade	Clinical outcome
0	No symptoms at all
1	No significant disability and able to carry out all duties
2	Slight disability. Unable to carry out some previous activities but able to look after own affairs without assistance
3	Moderate disability. Requiring some help but able to walk without assistance
4	Moderately severe disability. Unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability. Bedridden, incontinent and requiring constant nursing care and attention

Factors influencing on outcome after aSAH can be divided into patient factors, aneurysm factors, and institution factors.[4] Patient factors include the severity of the initial haemorrhage, age and sex of the patient, and medical comorbidities (e.g. hypertension, atrial fibrillation, coronary arery disease, congestive heart failure). Aneurysm factors include the size, location, and morphology of the ruptured aneurysm, and institutional factors include for instance the availability of surgical and endovascular services and the volume of aSAH patients treated.[146-149]

The severity and extent of the initial hemorrhage is the main determinant of clinical outcome after aSAH.[143,150] SAH is thought to reduce cerebral blood flow and decrease cerebral perfusion i.a. by inducing vasoconstriction and reducing cerebral autoregulation, activating microvascular collagenases and platelet aggregation, and by decreasing the availability of nitric oxide.[4,150-152] Recurrent hemorrhage, with a case fatality rate of approximately 70 %, is the most important treatable cause of poor outcome.[25,153] The risk of rebleeding is between 20 % and 30 % in the first month after aSAH and then stabilizes to a rate of approximately 3 % per year.[4,25] It has also been suggested that the risk of "ultraearly rebleeding" (i.e. within 24 hours of initial SAH) may be up to 15 %.[154-156] Of the institutional factors it has been observed that concentrating the care of aSAH patients to high-volume SAH treatment centers seems to improve the overall survival after aSAH.[146,148,149]

2.4 TREATMENT OF INTRACRANIAL ANEURYSMS

As approximately 20 to 30 percent of the ruptured aneurysms hemorrhage again within the first month after aSAH, the treatment of ruptured intracranial aneurysms is well grounded.[4,25] The management of unruptured cerebral aneurysms is, however, still much more controversial because of incomplete and conflicting data about the natural history of these lesions and the risks associated with their treatment. Based on the results of the ISUIA study, medical management and observation may be the best treatment method for many patients with unruptured small aneurysms especially in the anterior circulation.[36] On the other hand, the risk of small aneurysm rupture is not insignificant and the risk of aneurysm rupture should not be predicted on aneurysm size alone.[93] There seems to be a twofold to threefold increase in the risk of aneurysm rupture in Finnish (and Japanese) populations when compared to other populations, which supports the treatment of smaller unruptured aneurysms in Finnish population.[21,22] Many factors (i.e. the location, size, and morphology of the aneurysm as well as the method- and often age-specific risks of different treatment modalities) should be evaluated for each patient before initiating any treatment regimen for patients with unruptured cerebral aneurysms (see paragraph 2.2.1).

The operative treatment of intracranial aneurysms falls into two main categories, namely microsurgical treatment and endovascular techniques.

2.4.1 Microsurgical treatment

The first surgical ligation of an intracranial aneurysm was performed by Walter E. Dandy in 1937 and Yaşargil introduced the systemic use of noninvasive and atraumatic microsurgical techniques in the 1960s.[157-160] When an aneurysm is microsurgically clipped, the base of the aneurysm is closed by apposing the aneurysm walls which occludes the aneurysm completely and leaves the parent artery patent and unobstructed. The goal of microsurgical aneurysm treatment is to achieve complete and permanent exclusion of the aneurysm from the circulation while preserving the parent artery and possible perforating or branching vessels arising from the parent vessel. The complete closure of the aneurysm sac seems to be of pivotal importance in the prevention of rebleedings and regrowth of the aneurysm.[29,158,161]

Microsurgical operations are performed with the aid of a high magnification microscope, preferably with integrated near-infrared indocyanide green videoangiography (ICG-VA) which provides real-time information about the patency of branching vessels and about the aneurysm sac.[162,163] The refinement of skull base approaches provides an effective, targeted surgical field. Pterional, lateral supraorbital, orbitozygomatic, or the interhemispheric approach is used to access aneurysms in the anterior circulation while pterional, lateral suboccipital or subtemporal approach may be used to access posterior circulation aneurysms. The dissection of the aneurysm as well as adjacent vessel branches may be facilitated by the use of temporary clips. The duration of each temporary occlusion should be kept as short as possible (typically less than five minutes) to prevent parenchymal ischemia. Adequate dissection around the aneurysm base, properly sized and shaped occluding clip, and careful positioning of both of the blades of the clip are required to preserve the patency of the main vessel trunks and possible perforating branches. If the first clip slides or some of the aneurysm neck remains exposed, another clip may be introduced proximal to the previous one for final closure.[159,164-166] In addition to direct microsurgical clipping, aneurysm wrapping, trapping with or without bypass surgery, parent vessel clip reconstruction, endoaneurysmectomy, retrograde suction decompression, and other surgical methods may also be utilized especially in the surgical treatment of complex intracranial aneurysms.

The range of mortality and morbidity ranges reported in the surgical series is wide, periprocedural mortality varying from 0 % to 7 % and permanent morbidity varying from 4 % to 15.3 %.[3,167-170] In a meta-analysis of 2460 patients in 61 studies published between 1966

and 1996, procedure-related morbidity was 10.9 % and mortality 2.6 %.[170] In a recent study on clip ligation of unruptured intracranial aneurysms, the risk of poor surgical outcome was shown to be increased in patients presenting with age older than 60 years, ischemic cerebrovascular disease, posterior circulation aneurysms, presence of preoperative disability, and an aneurysm size of >25 mm.[171] Microsurgical therapy of giant and posterior circulation aneurysms is well documented[55,172-175], but especially in giant aneurysms surgical therapy may be challenging due to poor visibility to the neck of the aneurysm, the presence of a multitude of small perforating vessels (e.g. lenticulostriate, thalamostriate, and basilar perforating vessels), and occasionally due to large branches (e.g. M2 segments of the MCA) arising from the aneurysm sac.

The incidence of aneurysm remnant after microsurgical intervention varies from 1.8 % to 3.6 % even in specialized centers while parent artery occlusion is detected on postoperative angiography in 1.6 % to 21 % of the cases.[176,177] In a series of 808 surgically treated aneurysms, 12 % (97 of 808 aneurysms) of the clipped aneurysms were incompletely occluded, of which 61 % (59 of 97 aneurysms) were unexpected on postoperative angiograms.[158] Major vessel or branch occlusions were detected in 44 patients (5 %), 32 of which were unexpected. In a recent report of 246 procedures (232 patients and 295 aneurysms) performed with the aid of intraoperative ICG-VA, the clip position was modified intraoperatively as a consequence of ICG-VA in 9 % of the procedures (22 of 246), and in another 11 procedures (4.5 %) additional clips were applied due to observed residual aneurysm perfusion. Small (<2 mm) wide-necked aneurysm remnants were however missed in up to 10 % of patients and even a 6 mm residual aneurysm was missed by intraoperative ICG-VA in this study.[176] Based on these results, postoperative DSA imaging after aneurysm surgery seems justifiable even when surgeons have extensive experience with aneurysm surgery and have the highest technical standards available.

The relative proportion of aneurysms assigned into microsurgical and endovascular treatment varies considerably (from approximately 10 % up to 90 %) between centers and depends mainly on the experience of the attending neurosurgeons and interventional neuroradiologists. If either the microsurgical or the endovascular group is very small, some of the benefits of each treatment method are inevitably lost, and at least a few easier cases are also periodically required for each treatment category for practice and improving of the technique. Microsurgical clipping still represents the most efficient and durable treatment of for example unruptured MCA aneurysms, especially in the presence of a wide neck or if an arterial branch originates from the aneurysm neck.[178-181] Surgery is the main option of treatment also for many small cerebral aneurysms which are often difficult to treat by endovascular coil embolization.[182] In addition, the development of intracranial-intracranial bypasses is another important advancement that makes microsurgery a competitive option for the treatment of complex and recurrent cerebral aneurysms.[183-185]

Microsurgical aneurysm therapy is not only ethically defendable in view of the clinical outcome, but is also in line with a strategy to maintain and develop surgical experience within neurovascular centers. Technological advances (e.g. the development of endoscopic techniques, electrophysiological monitoring of the patient, the introduction of micro vascular Doppler ultrasonography, and the implementation of ICG-VA) have promoted surgical therapy in the same way as novel techniques (e.g. improved coils and flow-diverting stents) have revolutionized endovascular aneurysm therapy.

2.4.2 Endovascular treatment

The purpose of endovascular aneurysm therapy is to exclude the aneurysm from the circulation either by endosaccular occlusion or by flow diversion and parent vessel reconstruction. The endovascular approach to aneurysm occlusion has the theoretical advantage of avoiding craniotomy and brain manipulation, but is nevertheless associated with numerous challenges (i.e. the risk of periprocedural aneurysm rupture, occurrence of arterial dissections and/or thromboembolic complications, reactions to contrast material,

and puncture site complications). Since the initial publication of the results of the International Subarachnoid Aneurysm Trial (ISAT) in 2005, endovascular treatment of intracranial aneurysms has been firmly established.[153] In the ISAT study, 2143 patients with ruptured intracranial aneurysms admitted to 42 neurosurgical centers mainly in the UK and Europe, were randomly assigned either to neurosurgical clipping (*N*=1070) or endovascular coiling (*N*=1073). It was observed that in patients suitable for both treatments, endovascular coiling was more likely to result in independent survival at one year than neurosurgical clipping and that the survival benefit continued for at least seven years. The risk of rebleeding was low in both groups, but was more common after endovascular coiling than after neurosurgical clipping.[153] In the long-term follow-up of the ISAT study published in 2009, it was observed that there was an increased risk of recurrent hemorrhage from coiled aneurysms compared with clipped aneurysms, but the risks were small in both groups.[186]

The ISAT study has been criticised for biases regarding patient selection and center participation, as well as for differences in practitioner experience in the endovascular and microsurgical groups.[187-189] Considering these study limitations, the results of the ISAT study should not be directly extrapolated to all patients with ruptured intracranial aneurysms, and even less to unruptured aneurysms. The safety and efficacy of microsurgical clip occlusion and endovascular coil occlusion for the treatment of acutely ruptured cerebral aneurysms was also compared in the Barrow Ruptured Aneurysm Trial (BRAT). Based on mRS scores at three years, the outcomes of all patients assigned to coil embolization showed a favourable 5.8 % absolute difference compared with outcomes of those assigned to clip occlusion, but patients in the surgical group had a significantly higher degree of aneurysm obliteration and a significantly lower rate of recurrence and retreatment.[190] In the first published prospective randomized study comparing early endovascular and surgical treatment of ruptured cerebral aneurysms, the one-year clinical and neurophysiological outcomes in endovascular treatment were equal to the outcomes of acute surgical clipping of the ruptured aneurysm.[191] Endovascular treatment of the ruptured aneurysm was significantly less-often associated with MRI-detectable brain injury than surgical clipping, but was associated with a slightly poorer total occlusion rate of the aneurysm and with the need for repeated angiographic controls with possible re-embolization procedures (see paragraph 2.5). When long-term outcome of the brain was prospectively evaluated with MRI one year after endovascular or neurosurgical treatment for aSAH, parenchymal high-signal intensity lesions on T2- and intermediate-weighted MR images were more frequent after surgical treatment and lesion volumes also correlated with neuropsychologic test performance.[192]

2.4.2.1 Coil embolization

In endovascular coil embolization, a microcatheter is advanced into the aneurysm sac and the aneurysm is occluded with very soft detachable platinum coils of various sizes and shapes. Coil embolization was first introduced into clinical use in 1991 by Guglielmi et al. after the technology to produce microcatheters soft enough to navigate atraumatically into the aneurysm sac became available.[193,194] Since then, numerous different coils with special attributes (e.g. coils with different 2D or 3D morphologies; bioactive coils with polyglycolic acid, polyglycolic/polylactic acid, or hydrogel coating) have been developed.[195-198] While the safety profiles of bioactive coils seem comparable to those of bare platinum Guglielmi Detachable Coils (GDCs), superiority for either coil type is not established.[199] The evidence of sustained benefit of bioactive coils over bare platinum coils remained equivocal also in a review of the multiple trials and clinical series published on bioactive coils.[200]

The immediate angiographic result of aneurysm occlusion after coil embolization is often assessed with Raymond-Roy Occlusion Classification scale (Fig. 5). In this classification, residual neck (i.e. neck remnant) is defined as the persistence of any portion of the aneurysm of the original defect of the arterial wall as seen on any single projection but

without opacification of the aneurysm sac, whereas any opacification of the sac is classified as residual aneurysm and considered a failure of treatment.[201,202] While Raymond-Roy classification is useful in the evaluation of immediate angiographic results of aneurysm occlusion, it was not designed to predict recurrence rates.[203]

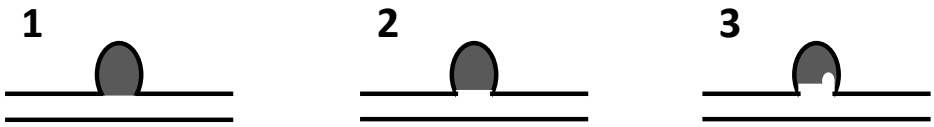

Figure 5. Classification of angiographic result after coil embolization by Roy et al. (Roy, Milot & Raymond 2001): class 1, complete occlusion; class 2, residual neck; class 3, residual aneurysm.

The morbidity and mortality rates associated with coil embolization of cerebral aneurysms depend markedly on many factors including the size and morphology of the aneurysm, target vessel anatomy, co-morbidities of the patient, and rupture status of the aneurysm. Usually the rate of adverse effects reported with coil embolization is approximately 10 % (8–21 %), of which less than half result in permanent clinical sequelae (1.0–5.2 %). Procedure related mortality rate ranges from 0.5 % to 1.7 % in larger, unselected series.[5,153,196,201,204-207] Of the major complications associated with coil embolization of intracranial aneurysms, thromboembolic complications are the most common. The estimated incidence of thromboembolism is in the range of 3–10 %, with permanent deficits in 3–5 %.[206,208,209] Puncture site complications are rare, with an incidence of less than 1 %.[204] Periprocedural aneurysm rupture occurs in about 3 %, and is more frequent in small (≤3 mm) and ruptured aneurysms.[210] Often the high risk of natural history of the aneurysm is associated with a high procedural risk (e.g. a giant basilar tip aneurysm would have a cumulative 5-year rupture risk of 50–60 % as well as a high periprocedural complication risk).[36]

2.4.2.2 Balloon-assisted embolization

The main factor limiting endovascular treatment of intracranial aneurysms is challenging morphology of the aneurysm sac. Endovascular treatment of wide-necked cerebral aneurysms is especially challenging since the coils used in the embolization may tend to protrude from the aneurysm sac into the parent artery. Moret et al. introduced in 1997 a novel technique to occlude wide necked cerebral aneurysms by temporarily inflating a non-detachable balloon in front of the aneurysm neck during each coil placement, a technique which the authors called "remodelling technique".[211] In this study, 56 aneurysms which were considered to be untreatable with conventional coil embolization due to wide-necked or otherwise challenging profile were selected for treatment with balloon-assisted embolization, and the remodelling technique allowed the treatment of 52 of these aneurysms with a low technique-related morbidity (1 of 52; 0.5 %) and mortality (0 of 52). The remodelling technique thus seemed to extend the spectrum of endovascularily treatable aneurysms without increasing the risk incurred by the treatment.

New, very compliant balloon-occlusion microcatheters have been subsequently developed, extending the usability of the remodelling technique to ever smaller vessels and more challenging arterial bifurcations, and the technique is now widely adopted.[212-217] A double-balloon remodelling technique has also been developed to allow the endovascular embolization of exceedingly broad-based bifurcation aneurysms (e.g. basilar artery bifurcation aneurysms).[218,219]

2.4.2.3 Conventional intracranial stents and stent-assisted embolization

Although coil protrusion into the parent artery may often be prevented with balloon-assisted remodelling technique, additional support or remodelling of the aneurysm neck is occasionally required. This can be achieved by deploying a stent over the aneurysm neck before coiling. Intracranial stents have been extensively studied, but the published data on stent-assisted coil embolization consists mostly of results in patients with nonruptured aneurysms treated in an elective setting.[8,9,220-230] The data on ruptured wide-necked aneurysms remains relatively scarce and the results of stent-assisted embolization in acute SAH are somewhat controversial.[12,222,228,231-234]

There are several theoretical advantages in using stents in the management of intracranial aneurysms: in addition to reducing the risk of coil protrusion into the parent artery, an intracranial stent provides a physical matrix for possible endothelial growth across the aneurysm neck and disturbs the inflow jet to the aneurysm sac, thus promoting aneurysm thrombosis. In an interesting study with an aneurysm model, Canton et al. showed that the use of flexible intravascular stent effectively reduced the strength of the vortex forming in an aneurysm sac and results in a decrease in the magnitude of stresses acting on the aneurysm wall.[235,236] Furthermore, the measured flow velocity and shear stress consistently decreased with the addition of each successive stent. Possibly due to this flow reduction and decrease in the shear stress in the aneurysm sac, deployment of an intracranial stent seems also beneficial with respect to reducing the recanalization rate of cerebral aneurysms.[10,237] In wide-necked aneurysms located at arterial bifurcations, narrowing of the bifurcation angle and additional support to the aneurysm neck may also be provided by the 'Y-stent' technique, whereby dual stents are deployed sequentially into each arterial branch.[238-240]

The Neuroform stent (Boston Scientific/Target Therapeutics, Fremont, CA, USA), a flexible, self-expanding, nitinol stent specifically designed for use in the cerebral vasculature, became available for aneurysm treatment in November 2002 and it was for many years the only available commercial stent for intracranial stenting. In recent years, however, many other stents have also been developed to address very specific challenges and to increase the number of aneurysms eligible for endovascular treatment. Although all of the conventional intracranial stents are laser-cut nitinol stents, the features of the stent vary depending on the profile and structure of the stent: it is generally accepted that stents with open cell design (i.e. adjacent cells formed by the strands of the stent are not interconnected) conform adequately also in tortuous vessels while stents with closed cell design (i.e. with adjacent cells interconnected) are usually re-sheathable and may have superior scaffolding across the aneurysm neck.

2.4.2.4 Flow-diverting stents

The clinical relevance of the flow diversion effect of intracranial stents was first discovered incidentally when aneurysm thrombosis was observed while performing staged stent-assisted aneurysm embolization by deploying a conventional intracranial stent across the aneurysm neck several weeks before the intended coiling of the aneurysm.[241,242] This flow-diversion effect is intensified with flow-diverting stents, which are specifically designed for the endovascular reconstruction of a segmentally diseased artery by redirecting the blood flow away from the aneurysm neck. Flow-diverting stents have a dense mesh geometry and a very high metal-to-surface coverage which induces stronger turbulence and flow reduction than that induced by conventional intracranial stents, potentially inducing thrombosis in the aneurysm sac. While the metal surface coverage of conventional intracranial stent is usually around 10 %, the dense mesh of flow diverting stents provide a metal surface area coverage of ca. 35 % to 55 %, depending on the stent size and parent vessel diameter. Therefore, flow-diverting stents represent a paradigm shift in the treatment philosophy for endovascular therapy of aneurysms from endosaccular occlusion, with the goal of flow redirection and parent vessel reconstruction.

The efficacy of flow-diverting stents was first demonstrated in several animal studies.[243,244] The results of the first larger clinical study (53 patients with 63 aneurysms treated with Pipeline Embolization Device [PED]) published by Lylyk et al. in 2009 were nothing short of revolutionary: complete occlusion of the stented aneurysm in 94 % of the patients within available follow-up with no major clinical adverse effects either periprocedurally or during the available follow-up period.[14] Reports of hemorrhagic and thromboembolic events associated with flow-diverting stents were however soon published, limiting the use of flow-diverting stents mostly to the endovascular treatment of complex intracranial aneurysms.[15-18]

The latest reports on flow-diverting devices have had variable and even somewhat conflicting results. Efficacy and favourable safety profile of flow-diverters has been shown in several well-designed studies[245-247], but on the other hand, in a recent, relatively large study of 80 patients with 84 flow-diverting stents, only 49 patients (58 %) had no complications while procedure-related mortality was 5.9 % and permanent new deficit was encountered in eight patients (9.5 %).[19] In smaller retrospective series flow-diverting stents have been successfully utilised also in the treatment of fusiform cerebral aneurysms[248], ruptured blister-like aneurysms[249], and treatment with a flow-diverting device has also been recommended as a primary treatment method for recurrent aneurysms.[247]

In a recent study of 178 patients treated either with a single PED (*N*=126) or multiple overlapping devices (*N*=52), complications occurred more frequently with multiple (15 %) versus a single device (5 %; *P*=0.03), and the use of multiple devices predicted complications also in multivariate analysis.[250] In this study, a significantly higher proportion of patients treated with a single device (97 %) achieved a favourable outcome compared with those treated with multiple devices (89 %, *P*=0.03). These findings suggest that treatment with a single flow-diverting device may be sufficient for treatment of most intracranial aneurysms and seems to provide similar occlusion rates with less complications and better overall outcomes than treatment with multiple overlapping stents.

2.4.2.5 Embolization with liquid embolic agent

A non-adhesive high-viscosity liquid embolic agent (Onyx; ev3 Neurovascular, Irvine, CA, USA) has also been used to treat cerebral aneurysms, with reportedly similar morbidity and mortality rates to those of other current endovascular techniques.[251-254] Onyx is comprised of 20 % ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO), and suspended micronized tantalum powder to provide contrast (i.e. visualization under fluoroscopy). When the material comes into contact with blood it precipitates and forms a soft polymer cast, which solidifies over a period of ca. 10 minutes.

In addition to allowing theoretically nearly 100 % volumetric occlusion of the aneurysm sac (as opposed to the optimal occlusion rate of ca. 30 % with coil embolization), Onyx induces reportedly intense neoendothelialization reaction which may lead to complete aneurysm exclusion from the circulation.[252,255,256] During Onyx injection, a remodeling balloon is typically inflated in the parent artery to protect it against leakage of the liquid embolic agent. The balloon must be intermittently deflated to allow cerebral reperfusion, and Onyx embolization conventionally involves repetitive cycles of balloon inflation and deflation.

In a prospective observational multicenter study conducted in 20 European centers, Onyx treatment was noted to offer a feasible endovascular treatment alternative for selected patients with aneurysms that were unsuitable for coil treatment or in whom previous treatment had failed to occlude the aneurysm.[253] In this study, aneurysm occlusion rates were reportedly superior to reported rates of coil occlusion for this subgroup of patients with either complete or subtotal occlusion in 65 of 71 aneurysms (92 %). Procedure- or device-related permanent neurologic morbidity was recorded in eight of 97 patients (8 %), procedure-related mortality rate was 2 % (2 of 97 patients), and delayed occlusion of the parent vessel occurred in nine patients.[253] Although complete aneurysm occlusion with

Onyx and protective devices and/or balloon remodeling technique seems feasible, migration of the liquid embolic agent into the parent artery remains a difficult challenge and the advent of flow-diverting stents has considerably decreased the use of Onyx in the treatment of complex intracranial aneurysms.[252]

2.4.2.6 Intrasaccular flow-disruption treatment

The WEB (Woven EndoBridge Cerebral Aneurysm Embolization Device; Sequent Medical, Aliso Viejo, CA, USA) is an intrasaccular ellipsoid braided-wire embolization device designed to provide blood flow disruption at the level of the aneurysm ostium.[257-259] The WEB demonstrated promising results in an experimental animal study[259], but the clinical data on the device remains scarce. In the biggest clinical series to date of 19 patients with 20 unruptured wide-necked bifurcation aneurysms treated by WEB placement, complete occlusion of the aneurysm was detected in two patients (11 %), near-complete occlusion in 15 patients (79 %), and incomplete occlusion in two patients (11 %).[257] Failure of the WEB placement occurred in one case (5 %) and a symptomatic neurological complication was encountered in two (11 %) cases. Further studies are needed to evaluate the indications, safety, and efficacy of this novel technique.

2.4.2.7 Covered stents (stent-grafts) in the treatment of intracranial aneurysms

Covered stents have also been used to treat intracranial (mainly distal ICA and VA) aneurysms with a high technical success, although the reported studies have mostly been based on single-center experiences.[260-264] In a small study of eight patients, covered stents have also been used safely and effectively to occlude recurrent aneurysms.[262] The main concern over using covered stents in the cerebral vasculature is the closure of side branches or perforating arteries originating from the covered arterial segment. Although the risk of side branch occlusion and subsequent stroke may be reduced by performing a balloon occlusion test prior to stent insertion, the risk of subsequent stroke is higher than with flow diverting devices.[260] While relatively good flexibility and efficacy of the stent have been reported in selected patients, the use of covered stents may also be limited due to the relative stiffness of the device and covered stents are not considered as the first-line treatment of intracranial aneurysms.

2.5 FOLLOW-UP AND RECURRENCE OF ENDOVASCULARLY TREATED ANEURYSMS

Aneurysm recurrence is relatively common after coil embolization, and the risk of aneurysm reopening is about 20 % in larger studies.[153,207,265-267] However, recurrence rates of up to 33.6 % have been reported, appearing at a mean time of 12.3 months after treatment (Table 5).[202] The durability of endovascular coil occlusion is thought to depend largely on the initial packing density achieved in the aneurysm sac, but coil compaction and aneurysm recanalization may occur even in aneurysms that appear completely occluded after the initial treatment.[198,268-271]

In the ISAT study, retreatment was 6.9 times more likely after endovascular therapy than after surgical clipping, the mean time to retreatment being 20.7 months.[266] Of 2143 patients randomly assigned to clipping or coiling, rebleeds from the treated aneurysm was detected in 13 patients, 10 of which in the endovascular group and three in the surgical group.[186] Since microsurgically treated aneurysms are usually not angiographically followed, the exact incidence of aneurysm regrowth after surgical treatment is unknown but seems to be low and associated with incompletely treated aneurysms with residual necks, which emphasizes the importance of optimal clip placement in the microsurgical aneurysm therapy.[158,272,273]

Retreatment of previously embolized aneurysms has on average a low complication rate and does not negate the advantage of the initial embolization.[274] Long-term monitoring of patients treated by endosaccular coiling seems mandatory, but the recommendable length of angiographic follow-up is not yet established. Increasing angiographic stability has been demonstrated in embolized aneurysms up to three years from coil embolization, suggesting follow-up angiography until this time.[275] In individuals with a family history of aSAH, the yield of long-term screening is however substantial even after more than 10 years of follow-up and two initial negative screens.[37], advocating longer angiographic follow-up in these cases.

Table 5. Overview of recurrence and retreatment rates of embolized intracranial aneurysms in observational studies.

Series	# of patients	# of aneurysms	Recurrence rate	Retreatment rate
Campi A et al. 2007	1096	-	-	17.4 %
Ferns SP et al. 2009	-	8161	20.8 %	10.3 %
Gonda D et al. 2014	944	-	-	20.4 %
Henkes H et al. 2008	2360	2759	-	12.3 %
Raymond J et al. 2003	466	501	33.6 %	20.7 %

The durability of coil occlusion of intracranial aneurysms is thought to depend on density of packing (volume embolization ratio) achieved within the aneurysm sac.[198,269,271] Although initial angiographic occlusion may be suboptimal for determining aneurysm recurrence after embolization, measurement of volume embolization ratio (calculated by dividing the volume of the embolized coils by the volume of the aneurysm) is useful in predicting angiographic changes of embolized aneurysms. In the calculation of volume embolization ratio coils are considered to be long cylinders (i.e. volume of coil = π x [diameter of coil / 2]^2 x length of coil) and the aneurysm sac is assumed to be an ellipsoid (i.e. volume of aneurysm = 4π / 3 x [aneurysm width / 2]^2 x [aneurysm length / 2]^2 x [aneurysm height / 2]^2). High volume embolization ratio (and low risk of recanalization) is usually easier to achieve in small aneurysms with a narrow neck than in larger, wide-necked aneurysms.[269-271]

3 *Aims of the study*

The purpose of this study was

I To evaluate the safety and efficacy of stent-assisted embolization of ruptured wide-necked intracranial aneurysms in the acute phase (<72 h) of SAH.

II To assess the usability and efficacy of stent-assisted embolization in the treatment of recurrent or residual intracranial aneurysms.

III To evaluate the usability of flow-diverting stents in the treatment of complex intracranial aneurysms.

4 *Materials and methods*

4.1 PATIENT SELECTION AND ANEURYSM CHARACTERISTICS

A retrospective, observational cohort design was adopted in all of the studies [I-III]. The study population consisted of all of the patients treated either with stent-assisted embolization or with a flow-diverting stent in three tertiary care centers in Finland (Kuopio University Hospital, Tampere University Hospital, and Turku University Hospital) during the study period. The treated aneurysms were either wide-necked (width of the neck ≥4 mm or dome-to-neck ratio ≤2; [I-II]) or otherwise complex aneurysms or focal vascular pathologies [III] not eligible for conventional or balloon-assisted embolization therapy (Fig. 6). The form of treatment of the aneurysm was individually evaluated via a consensus between an experienced neurosurgeon and an interventional radiologist or neuroradiologist. The estimated risks of various retreatment options were weighed against the estimated risk of aneurysm rupture, and the patients were informed about the treatment options and their estimated risks.

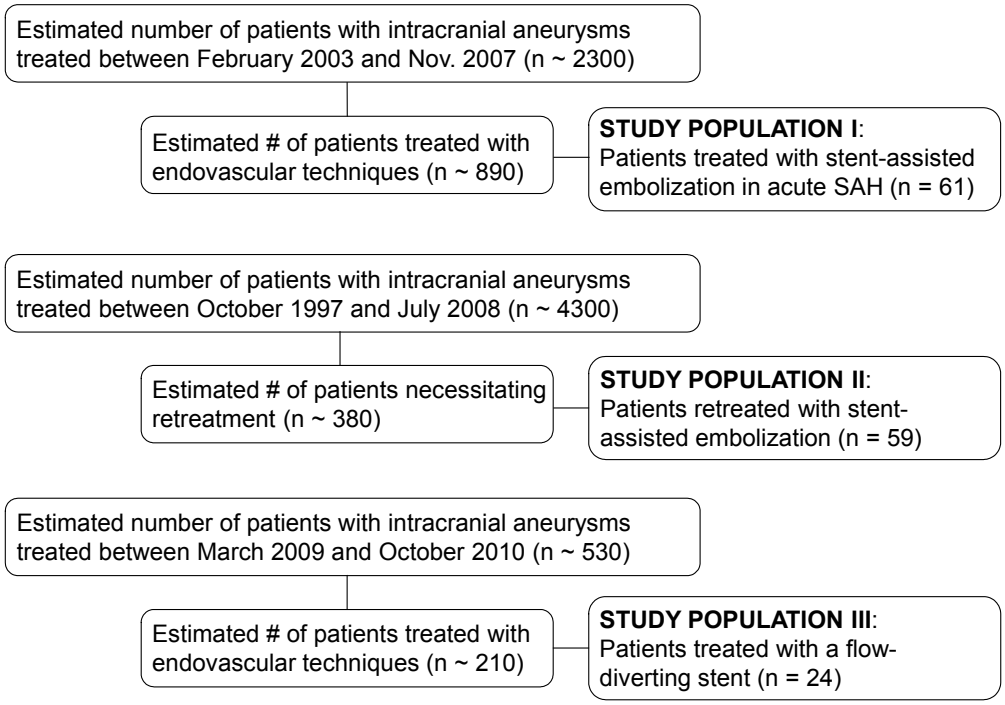

Figure 6. Patient selection flowchart.

4.1.1 Stent-assisted embolization of ruptured aneurysms in acute SAH [I]

All patients with ruptured wide-necked cerebral aneurysms who were treated with stent-assisted coil embolization in the acute phase (<72 hours) of SAH in three tertiary care centers (Kuopio University Hospital, Tampere University Hospital, and Turku University

Hospital) during the study period (February 2003 to November 2007) were included in the study. The retrospective evaluation of the patient records and all angiographic data was finished in June, 2008. The study population consisted of 20 men and 41 women with a mean age of 55.1 years (range 26–83 years), including five patients (8 %) in whom the procedure was unsuccessful due to the difficult target anatomy and tortuosity of the arteries.

Endovascular treatment was often favored over surgical ligation in older patients and in patients with poor clinical condition, although in comatose or moribund patients some signs of clinical recovery were expected before initiating active endovascular treatments. Surgical treatment, on the other hand, was often preferred for young patients with anterior circulation aneurysms, or if the patient presented with a large parenchymal hematoma. All of the treated aneurysms had a wide-necked profile (i.e. neck width of more than 4 mm or dome-to-neck ratio of less than 2). A slight majority of the aneurysms (33 of 61; 54 %) were located in the posterior circulation, and two (3 %) of the ruptured aneurysms located in the vertebral artery were considered to be dissecting aneurysms. The largest diameter of the treated aneurysm ranged from 2 mm to 19 mm (mean 6.7 mm), and none of the ruptured aneurysms in this series had been previously treated.

Technical success of the procedure was recorded if the ruptured aneurysm was successfully stented and embolized with a satisfactory angiographic result (complete [>95 %] angiographic occlusion or a small neck remnant with angiographic occlusion rate of >80 % and contrast medium filling only the neck area of the aneurysm).

4.1.2 Stent-assisted embolization of recurrent or residual cerebral aneurysms [II]

The patient records and angiographic data for all consecutive patients with recurrent or residual cerebral aneurysms treated with stent-assisted coil embolization in three tertiary care centers in Finland (Kuopio University Hospital, Tampere University Hospital, and Turku University Hospital) from February 2003 to June 2011 were retrospectively analyzed. A total of 59 patients with 60 treated aneurysms were identified, of whom four patients treated either in the acute phase (≤72 h; *N*=2) or late subacute stage (<4 weeks; *N*=2) of SAH were excluded, resulting in a study group of 55 patients with 56 aneurysms (17 men and 38 women; mean age 51.5 years). The aneurysms included in the study had been initially treated either by coil embolization (51 of 56; 91 %) or surgical ligation (5 of 56; 9 %) between October 1997 and July 2008.

Unstable recurrent aneurysms with designated growth of the recurrence size during follow-up were typically selected for retreatment, and previously ruptured aneurysms were more likely retreated than nonruptured aneurysms. Aneurysm recurrences less than 2 mm in diameter were not retreated due to the low risk on rebleeding and the difficulty of the reembolization procedure, whereas recurrences exceeding 4 mm in diameter were usually selected for retreatment although the size of recurrence necessitating retreatment depended considerably on the size and shape of the initial aneurysm. The largest diameter of the recurrent or residual portion of the aneurysm varied from 2 mm to 20 mm (mean 5.5 mm) in this series while the largest diameter of the entire aneurysm ranged from 4 mm to 27 mm (mean 10.4 mm). Most of the patients (45 of 55; 82 %) had a history of SAH, the time interval between SAH and stent-assisted embolization of the aneurysm varied from eight weeks to over 10 years.

Technical success of the procedure was recorded if the recurrent or residual aneurysm was successfully stented and re-embolized with a satisfactory initial angiographic result with either complete occlusion or a small residual neck. The angiographic results were categorized into primary angiographic success (adequate occlusion and stability of the stented aneurysm without additional therapies), secondary angiographic success (adequate occlusion and stability of the aneurysm achieved by additional therapies), and angiographic failure (residual aneurysm and/or instability of the treated aneurysm).

4.1.3 Flow-diverting stents in the treatment of complex intracranial aneurysms [III]

Technical results and follow-up data on 24 consecutive patients (20 female and four male, with a mean age of 55.3 years [range 43–70 years]) treated with 29 flow-diverting stents in two tertiary care centers (Kuopio University Hospital and Tampere University Hospital) between March 2009 and October 2010 were retrospectively evaluated. Stented vascular pathologies included diffuse fusiform aneurysms (4 of 24; 17 %), neck remnants of previously treated aneurysms (10 of 24; 42 %), wide-necked saccular aneurysms (6 of 24; 25 %), and multianeurysm complexes (4 of 24; 17 %). The stent placement was performed in two patients (8 %) in the acute phase (<72 hours) of SAH, in two patients (8 %) in the subacute phase (3–7 days) of SAH, and in addition, 6 of the 20 electively treated patients had a previous history of SAH.

Treatment with a flow-diverting stent was selected only if surgical ligation, sacrifice of the parent artery, and endovascular embolization of the aneurysm were considered infeasible due to the difficult location and/or morphology of the aneurysm.

Technical success of the procedure was analyzed by evaluating the delivery of the flow-diverting stent to the intended vascular pathology, the patency of the parent artery after stent insertion, and possible adjunctive therapies. Primary technical success was recorded if the flow-diverting device was successfully and without complications delivered across the neck of the aneurysm with a fully patent and unobstructed parent artery, while assisted primary technical success was recorded if delivery of the stent and unobstructed parent artery were achieved with adjunctive medical therapies (ie. peri-interventional balloon angioplasty, delivery of additional stents, or medical treatment of perioperative thromboembolic events).

4.2 ENDOVASCULAR PROCEDURE

4.2.1 Conventional stent-assisted embolization [I-II]

A 90-cm guiding catheter (Boston Scientific, Fremont, CA, USA) was inserted to the relevant carotid or vertebral artery and a microcatheter (Excelsior SL-10; Boston Scientific/Target Therapeutics, Fremont, CA, USA) was navigated past the aneurysm with the help of a standard micro guidewire. After the deployment of the stent (Neuroform; Boston Scientific/Target Therapeutics), the aneurysm was usually embolized with the microcatheter placed through the stent interstices, although in a few cases the microcatheter was positioned ('jailed') in the aneurysm before stent deployment. After stenting, the recurrent or residual aneurysms were packed with GDCs and/or Matrix coils (Boston Scientific) in earlier phase of the studies and with Target (Stryker Neurovascular, Fremont, CA, USA) or Axium coils (ev3 Neurovascular, Irvine, CA, USA) in later cases. The Neuroform stent used exclusively in the original communications I and II is a laser cut nitinol stent with a semi-open cell structure.

All of the patients treated in the acute phase of SAH were heparinized (Heparin LEO; Leo Pharma, Ballerup, Denmark) during the procedure, with the aim of achieving measured activated clotting times (ACTs) of about 250 seconds. The heparinization was usually initiated after the first coil or coils had been deployed and the ruptured aneurysm was considered to be stable. Intravenous acetylsalicylic acid (250–500mg) was administered perioperatively to a majority of the patients (43 of 61; 70 %), and a combination therapy with clopidogrel bisulphate (Plavix; Sanofi Pharma Bristol-Meyers Squibb, Paris, France), with a loading nose of 300 mg and a daily dose of 75 mg for 1–3 months postoperatively and acetylsalicylic acid (100 mg daily for 3–6 months) was started immediately after the procedure.

In the electively treated patients, the dual antiplatelet therapy with clopidogrel bisulphate (75 mg daily) and acetylsalicylic acid (100 mg daily) was initiated prior to the procedure. Response to clopidogrel bisulphate was confirmed via the VerifyNow system (Accumetrics, San Diego, CA, USA) after this device became available in our centers in

January 2010 and additional doses of clopidogrel bisulphate or prasugrel hydrochloride (Efient; Eli Lilly Nederland BV, RA Houten, The Netherlands) were administered when necessary. All of the patients were periprocedurally heparinized with an ACT target of about 240 seconds and dual antiplatelet therapy with clopidogrel bisulphate (75 mg daily for 3 months) and acetylsalicylic acid (100 mg daily for a minimum of 6 months) was continued postprocedurally.

4.2.2 Endovascular procedure with a flow-diverting device [III]

A microcatheter with an inner diameter of 0.60 mm (Vasco + 21 MP; Balt Extrusion, Montmorency, France) was navigated past the aneurysm neck the help of a microguidewire (Transend EX or Synchro2 Standard; Boston Scientific, Fremont, CA, USA) and a 6F Envoy guiding catheter (Cordis Neurovascular; Miami Lakes, FL, USA). The flow-diverting stent (Silk; Balt Extrusion, Montmorency, France), which is composed of 48 nickel-titanium (nitinol) alloy and platinum filaments that provide a metal to surface area coverage of ~35 %, was thereafter deployed over the intended vascular pathology with a combination of careful pressure on the delivery wire and retraction of the microcatheter. The stent was carefully manipulated to achieve full opening and the stent was usually recrossed with the delivery catheter after deployment to ensure adequate wall apposition as recommended by the manufacturer. In four (17 %) of the later cases, the aneurysm was loosely packed with GDCs before stenting.

4.3 FOLLOW-UP

Follow-up imaging was primarily performed by DSA. In addition, MR angiography (contrast enhanced and three dimensional time-of-flight MR angiography) was occasionally utilized in studies I and II if the initial angiographic result was adequate and the risk of aneurysm recurrence was small, or if adequate angiographic result and stability of the treated aneurysm had already been confirmed in preceding DSA follow-up images. The small imaging artifacts caused by the markers at both ends of the Neuroform stent only rarely interfered with the interpretation of the MR angiograms.[276-280]

4.4 STATISTICAL METHODS

The statistical analysis was performed with IBM SPSS Statistics (SPSS Inc., Chicago, IL, USA). Dichotomous and other categorical variables were compared with the χ^2 test or Fisher's exact test, and the Mann-Whitney *U* test and Kruskal-Wallis one-way analysis were used to compare continuous-scale data for non-normally distributed variables [I-III]. Continuous-scale data was also frequently categorized to subgroups to facilitate statistical analyses. In the original communication III, a binomial regression analysis was also performed after univariate analyses. *P* value of less than .05 was usually considered to indicate a statistically significant difference.

4.5 ETHICAL ISSUES

The present study was approved by the institutional review board of Tampere University Hospital. Due to the retrospective nature of the study, the need to obtain informed consent was waived.

5 Results

5.1 STENT-ASSISTED EMBOLIZATION IN ACUTE SAH [I]

5.1.1 Technical success and initial angiographic results

The technical success rate was 72 % (44 of 61 patients), and an adequate primary angiographic result with either complete occlusion of the aneurysm or a small neck remnant was achieved in 64 % (39 of 61 patients) (Fig. 7). In six (10 %) patients, the delivery of the stent failed due to the excessive tortuosity of the target artery. After stent deployment, coiling of the stented aneurysm was in addition unsuccessful in three (5 %) patients due to the small size of the aneurysm (dome height, 2 mm) and in two (3 %) patients because of unfavorable anatomy of the aneurysm.

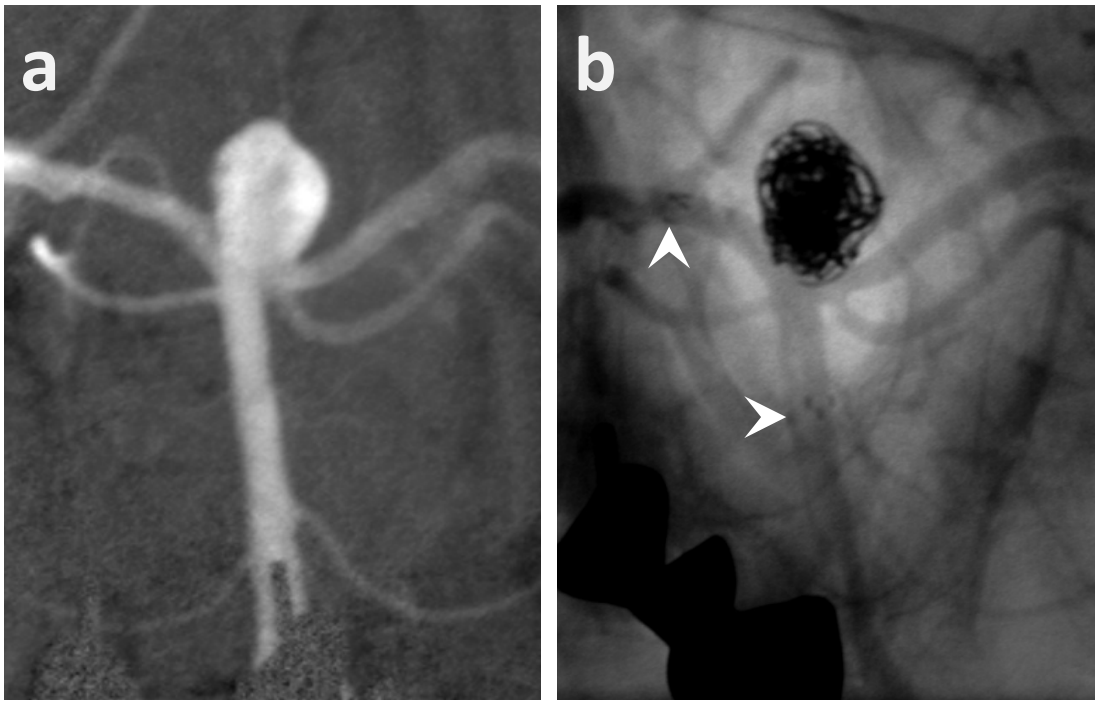

Figure 7. A DSA image of a wide-necked ruptured basilar tip aneurysm before *(a)* and after *(b)* stent-assisted embolization of the aneurysm. A complete occlusion of the aneurysm was achieved in this case. The proximal and distal markers of the stent (Neuroform 3.5/15 mm) are indicated by arrowheads.

5.1.2 Complications

Procedure-related major complications were encountered in 13 of the 61 patients (21 %). The major complications included aneurysm perforation in four (7 %) patients, thromboembolic events in seven (11 %) patients, one case of early rebleeding from the aneurysm combined with vasospasm, and one puncture site pseudoaneurysm which was successfully treated with US-guided thrombin injection. Periprocedural thromboembolic complications were routinely treated with intraarterial abciximab (ReoPro; Contocor,

Leiden, The Netherlands) together with heparin and five of the seven patients with thromboembolic events had adequate recovery with GOS scores of 4–5 at the end of the study period.

5.1.3 Follow-up data and clinical outcome

The mean duration of angiographic follow-up was 12.1 months with a range from 0 to 52 months. Reembolization of the stented aneurysm was performed in four patients (7 %), either due to initial suboptimal occlusion of the stented aneurysm (*N*=1; 2 %), or due to coil compaction and recanalization of the treated aneurysm (*N*=3; 5 %). The total mortality rate was 21 % (13 of 61 patients), with 30-day mortality rate of 20 % (12 of 61). This large perioperative mortality rate is partially explained by the poor preoperative clinical condition of some of the patients and severe nature of aneurysmal SAH. After the primary phase the risk of mortality and morbidity decreased considerably, and most of the patients made good recoveries with 42 of the 61 patients having a Glasgow Outcome Scale score of 4 or 5 at the end of the study period. Patient demographic data, aneurysm characteristics, or primary angiographic result did not significantly correlate with the clinical outcome.

5.2 STENT-ASSISTED EMBOLIZATION OF RECURRENT OR RESIDUAL ANEURYSMS [II]

5.2.1 Technical success

The technical success rate was 91 % (50 of 55 patients). In one patient (2 %), the delivery of the intracranial stent failed due to tortuosity of target artery, and in four patients (7 %) adequate coil embolization was not achieved after stenting.

5.2.2 Adjunctive therapies and procedural complications

Complications were encountered in six patients (11 %), including perioperative aneurysm perforation in three patients (5 %), progressive brain stem compression symptoms after the embolization of a large basilar tip aneurysm in two patients (4 %) (Fig. 8), and postoperative retroperitoneal and intra-abdominal hemorrhage in one patient (2 %). Complications resulted mainly in unfavorable clinical outcome and only the patient with retroperitoneal and intra-abdominal hemorrhage recovered without clinical sequelae.

In addition to procedural complications, periprocedural adjunctive therapies were required in five patients including the treatment of minor periprocedural thromboembolism with intra-arterial abciximab in two patients (4 %), stenting of presumable iatrogenic vertebral dissections in two patients (4 %), and insertion of an additional intracranial stent due to suboptimal placement of the primary stent in one patient (2 %). None of these five patients had post-procedural clinical sequelae.

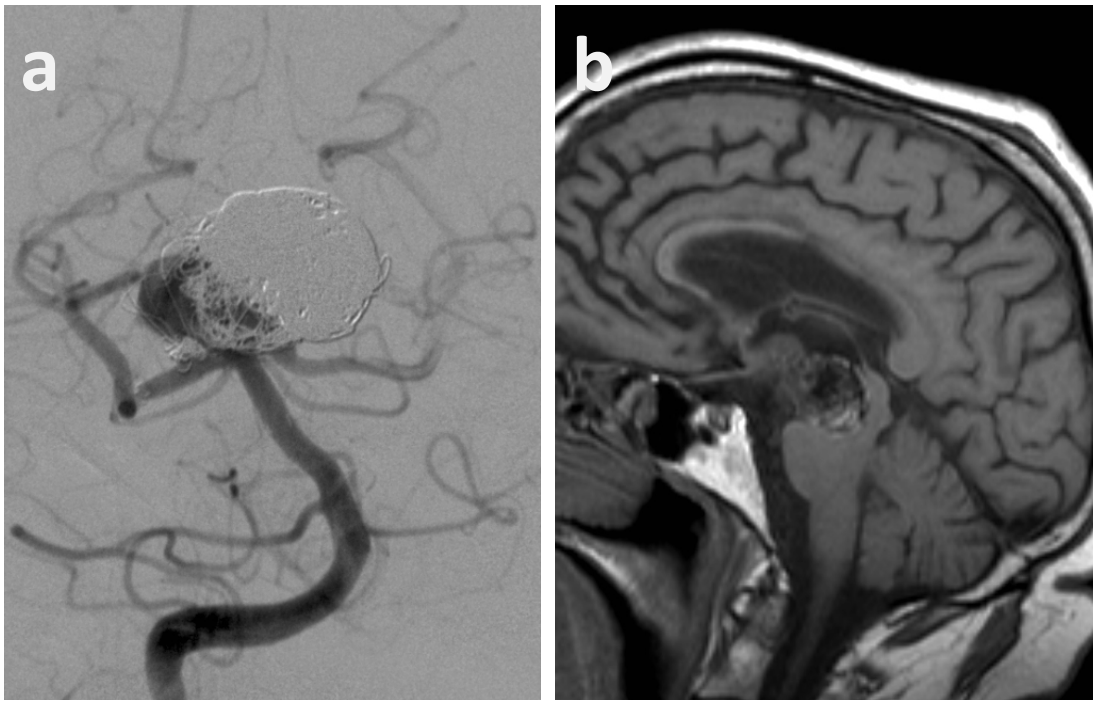

Figure 8. A marked recanalization is observed in a DSA image *(a)* obtained 30 months after stent-assisted re-embolization of a giant basilar tip aneurysm. In spite of five successive endovascular treatment attempts, permanent occlusion of the recurrent aneurysm was not achieved and the patient developed brain stem compression symptoms as seen in a T1-weighted MRI image *(b)*; the patient died within one month.

5.2.3 Follow-up data and clinical outcome

Angiographic and clinical follow-up data were available for 51 patients with 52 aneurysms (93 %), with a mean follow-up time of 28.1 months (range 3–114 months). Additional endovascular treatment sessions were performed in nine patients (16 %), either due to coil compaction and recanalization of the recurrent aneurysm (*N*=7; 13 %) or due to suboptimal initial occlusion of the treated aneurysm (*N*=2; 4 %).

The clinical outcome was favorable in 50 of 55 patients (91 %), while poor clinical outcome was recorded in five (9 %) patients. Perioperative mortality rate was 2 % (*N*=1). Statistically significant correlations were found between poor clinical outcome and giant (>25 mm) total aneurysm size (*P*=0.002), a large (>10 mm) recurrent aneurysm size (*P*=0.011), and the occurrence of periprocedural complications (*P*<0.001) (Table 6). Since there was a strong intercorrelation between recurrence size and total aneurysm size (*P*=0.006) in a binomial regression analysis, the only independent factor related to poor clinical outcome was the occurrence of periprocedural complications (*P*=0.017).

Table 6. Factors associated with clinical outcome after stent-assisted embolization of recurrent or residual aneurysms.

	***P* value**[a]
Total aneurysm size	*0.002*
Recurrent/residual aneurysm size	*0.011*
The occurrence of periprocedural complications	*<0.001*
Administration of adjunctive medical therapy	1.000
Initial post-operative angiographic result (complete occlusion; neck remnant; partial occlusion / no coiling)	0.669
Number of previous treatment sessions (1; 2-4; ≥5)	0.104
History of SAH	1.000

5.3 FLOW-DIVERTING STENTS IN THE TREATMENT OF COMPLEX CEREBRAL ANEURYSMS [III]

5.3.1 Technical success

The primary technical success of the procedure was 67 % (16 of 24 patients). In addition, assisted primary technical success was recorded in five patients (21 %). Technical failure was recorded in three patients (13 %): the flow-diverting stent could not be deployed due to difficult target vessel anatomy in one patient (4 %); the stent remained partially tapered regardless of balloon angioplasty in one patient (4 %); and a delayed major ischemic complication was encountered in one patient (4 %) and was regarded as a technical failure although the initial angiographic result was desirable.

5.3.2 Complications and periprocedural adjunctive therapies

Periprocedural adjunctive therapies were administered in six patients (25 %), including three (13 %) cases where additional balloon angioplasty was required to open the flow-diverting stent fully and 1 case (4 %) where a closed-cell stent (Enterprise; Cordis Endovascular, Miami Lakes, FL, USA) was placed inside the flow-diverting stent to ensure the patency of the device. In two of these cases, the transitory flow obstruction caused by the incompletely opened flow-diverting stent resulted in thromboembolism necessitating administration of intra-arterial abciximab (ReoPro; Contocor, Leiden, The Netherlands). Altogether, periprocedural thromboembolism was treated with intra-arterial abciximab in four patients (17 %), none of whom developed permanent neurological sequelae. Procedural complication and mortality rates were 4 % (1 of 24; a fatal ischemic stroke within 24 hours from the procedure).

5.3.3 Follow-up data and clinical outcome

Follow-up data was available for twenty patients (83 %; 23 aneurysms and 24 stents), with a mean angiographic follow-up time of 9.0 months (range 2–17 months). Complete occlusion of the stented aneurysm was observed in 16 of 23 stented aneurysms in 16 patients (70 % and 80 %, respectively) (Fig. 9). In four aneurysms (17 %), the flow-diverting stent had not induced thrombosis and the aneurysms remained unsecured. Follow-up of these patients is continuing and further treatment options will be individually considered based on the

longer term follow-up images. In addition, follow-up imaging revealed asymptomatic stenosis (*N*=1) and occlusion (*N*=1) of the stented artery in two patients (10 %).

The clinical outcome was favorable in majority of the patients, with a GOS score of 4 or 5 in 22 of 24 patients (92 %) at the end of the study period. A GOS score of 3 was recorded in one (4 %) patient and a GOS score of 1 in one (4 %) patient, both of whom were in the acute or subacute SAH group. There was a statistically significant correlation with poor clinical outcome and acute or subacute SAH (*P*=0.022; Fisher's exact test), but statistical analyses were subsequently removed due to the small amount of patients in the (sub)acute SAH group.

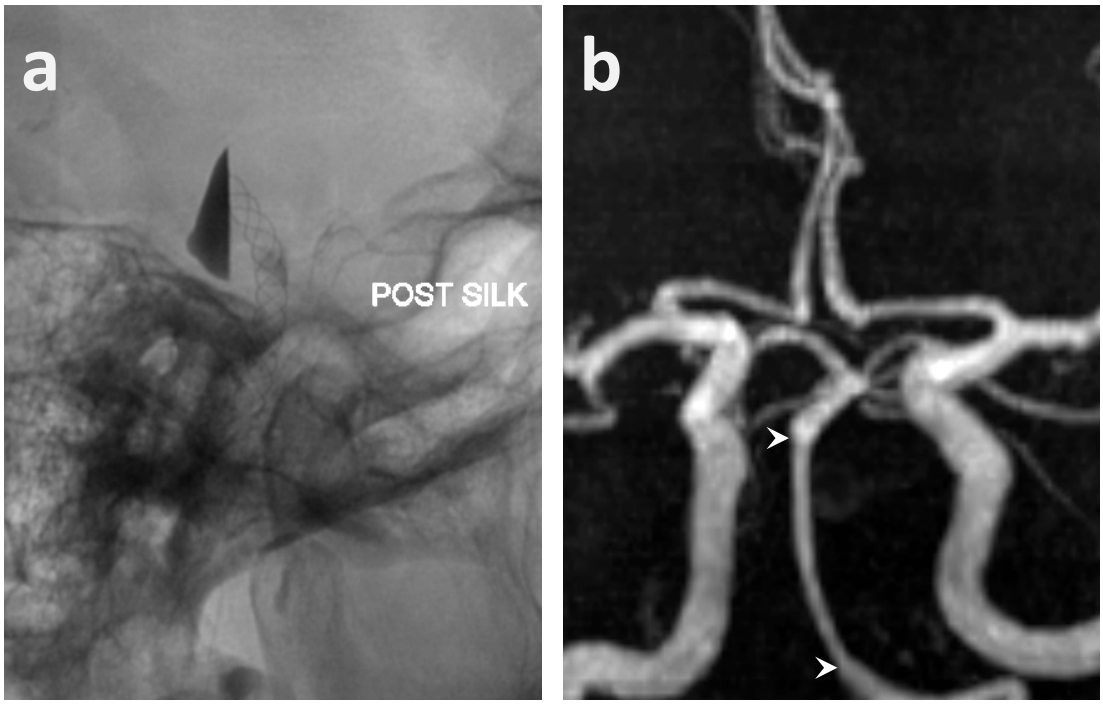

Figure 9. A large basilar tip aneurysm was treated with a flow-diverting stent (Silk 3.5/25 mm) which is well visible in a perioperative DSA image *(a).* Note the stasis of the contrast material within the aneurysm sac indicating the hemodynamic changes induced by the stent. Occlusion of the aneurysm and patency of the parent vessel may be assessed in a follow-up TOF-MRA image acquired at six months *(b)*, although a slight narrowing of the stented segment (indicated by arrowheads) is induced by the ferromagnetic bands of the stent.

6 Discussion

The rapid development of intracranial stents has revolutionized the management of intracranial aneurysms and has enabled the treatment of many previously untreatable cerebral aneurysms. However, many limitations and challenges still persist, and stent-assisted embolization is far from being a panacea in the treatment of complex intracranial aneurysms. Due to the lack of long-term knowledge on the risks of arterial injury or stenosis after stent deployment, aneurysm recurrence, or even the risk of stent fracture, all intracranial stents should be used very selectively on younger patients with a substantial life expectancy.[180] The complications and adverse outcomes encountered in this study emphasize the relevance of the operator's expertise, the importance of adequate antithrombotic medical therapy, and the pivotal role of proper patient selection. It is also worth noticing that the retrospective study cohorts presented in this study consist of first generation stents and flow diverting devices at the earliest phase of the learning curve.

As stated in an excellent review on treatment strategies for complex intracranial aneurysms, perhaps the most significant breakthrough in the management of complex intracranial aneurysms in recent years has been the complementary interaction of endovascular and surgical technologies and the waning of the coil versus clip controversy.[7] Optimal treatment of cerebral aneurysms requires the availability of both experienced cerebrovascular surgeons and interventional neuroradiologists working in a collaborative effort to tailor an individual treatment plan for each patient. In addition, acute aSAH is a complex and multifaceted disorder and many of the aSAH patients require a prolonged treatment in the intensive care unit. The management of aSAH patients focuses also on the anticipation, prevention and management of secondary complications (i.e. rebleeding from the aneurysm, hydrocephalus, seizures, cardiopulmonary complications, and delayed cerebral ischemia), and favourable outcomes are more likely in institutions that treat high volumes of patients with aneurysmal SAH.

6.1 DISADVANTAGES OF ENDOVASCULAR ANEURYSM THERAPY

In addition to the technique-related limitations of endovascular treatment methods discussed in detail in Chapter 2, there are several additional perspectives that should be considered when evaluating endovascular techniques against microsurgical aneurysm therapy. Firstly, the cost of novel endovascular devices exceeds vastly the cost of microsurgical clips. While the price of a microsurgical clip is usually at most a few hundred euros, all of the intracranial stents are priced in several thousand euros and the price of flow-diverting devices often exceeds 10 000 euros. It remains to be seen whether the price of endovascular devices will eventually drop when the number of manufacturers increases and the market becomes saturated.

Secondly, the use of intracranial stents necessitates antithrombotic medication. The guidelines for antiplatelet therapy after stent-assisted embolization are based on cardiology experience, and recent cardiology guidelines recommend administration of acetylsalicylic acid indefinitely after coronary stenting, whereas clopidogrel bisulphate is usually administered for 12 months.[281] In intracranial stents, however, aneurysmal factors should also be considered. Incomplete aneurysm occlusion may produce a dead space in combination with the stent, resulting in continual flow disturbance and becoming a long-term embolic source. Delayed ischemic stroke after stent-assisted embolization seems to be

associated mainly with insufficient duration of dual antiplatelet therapy rather than inadequate platelet inhibition.[282] While short-term combination therapy of clopidogrel bisulphate and acetylsalicylic acid is effective and safe for stroke prevention even in high vascular risk patients, long-term combination therapy increases the risk of intracranial hemorrhage and major bleeding substantially.[283-285] Therefore, the duration of dual antiplatelet therapy should probably be tailored to clinical status, co-morbidities, and angiographic outcome of each patient.

Thirdly, endovascular aneurysm treatment almost invariably necessitates long-term angiographic follow-up. Aneurysm recurrence is common after coil embolization (see paragraph 2.5), and routine angiographic follow-up imaging for a minimum of three years after aneurysm embolization has been recommended.[275] It is also worth noticing that there is, as yet, no information on long-term or lifetime efficacy and safety of stent-assisted embolization, advocating very long clinical and angiographic follow-up after stent-assisted aneurysm treatment.

6.2 STENT-ASSISTED EMBOLIZATION OF ACUTELY RUPTURED WIDE-NECKED ANEURYSMS [I]

Early treatment of the ruptured aneurysm is usually well-grounded due to the high risk of subsequent rerupture of the aneurysm.[85] Acute SAH is, however, a hypercoagulable state in which the tendency for thrombosis is high, which correspondingly increases also the risk of both perioperative thromboembolic events and the risk of parent vessel occlusion after the stent deployment. It may even be argued that stent-assisted aneurysm embolization in acute SAH has little in common with stent-assisted aneurysm embolization in an elective setting, and that the use of stent-assisted embolization in the acute SAH remains somewhat controversial despite positive results reported in a few limited series.[12,286]

In a systematic review of published data on stent-assisted coiling in acutely ruptured intracranial aneurysms, it was suggested that adverse outcomes are more common in stent-assisted coil embolization in acutely ruptured aneurysms compared with similar grade acutely ruptured aneurysms treated by coil embolization alone.[232] Furthermore, in a recent study of 72 patients with ruptured wide-necked aneurysms treated with stent-assisted coil embolization in acute SAH, microsurgical clipping or endovascular treatment with another technique (i.e. multiple microcatheter or balloon assisted technique) was advocated due to the high complication rate (19.4 %; 14 of 72 patients) observed in the study.[231] Stenting is, however, known to stabilize and improve the anatomical results of coil embolization especially in wide-necked aneurysms in which unassisted or even balloon-assisted embolization may prove infeasible. The controversial results on stent-assisted embolization of acutely ruptured cerebral aneurysms reflect the difficulties encountered in the therapeutical decisions in the setting of acute SAH, and the optimal patient selection for each treatment method in the acute phase of SAH is still open to discussion.[286]

Aggressive periprocedural heparinization and preprocedural dual antiplatelet therapy with clopidogrel bisulphate and acetylsalicylic acid routinely administered in the stent-assisted embolization of nonruptured aneurysms are contraindicated in the setting of acute SAH. Heparinization was typically initiated in our study after the first coil or coils had been deployed to the aneurysm sac and the ruptured aneurysm was considered to be stable, although small amounts of heparin were administered from the beginning of the procedure in the continuous rinsing infusion of the catheters. Combination therapy with clopidogrel bisulphate and acetylsalicylic acid was started immediately after the procedure. The highly operator-dependent delay in the initiation of adequate antithrombotic therapy – in a hypercoagulable state with an increased risk of thromboembolism – heightens the importance of the smooth, undelayed course of the procedure. In the setting of ruptured wide-necked bifurcation aneurysms, treatment with an intrasaccular flow disruption device

(WEB) might be feasible since it seems to offer reasonable aneurysm stability and occlusion rate without the need for subsequent dual antiplatelet therapy.[257]

The complication rate in our study was higher than was reported in several series of stent-assisted embolization of wide-necked cerebral aneurysms treated almost invariably in an elective setting.[9,220-223] Our results are, however not directly comparable to these studies because of the excess mortality and morbidity associated with acute SAH. In addition, the patient population was highly biased due to the selective nature of our study and difficult-to-treat posterior fossa aneurysms were markedly over-represented in our series. When compared to the baseline results set by the ISAT study, in which 250 of 1063 patients (23.5 %) with ruptured intracranial aneurysms allocated to endovascular treatment were dead or dependent at 1 year, our results are directly comparable with 13 of 61 patients (21.3 %) dead or dependent at 12.1 months.[153]

6.3 STENT-ASSISTED EMBOLIZATION OF RECURRENT OR RESIDUAL CEREBRAL ANEURYSMS [II]

Coil compaction and aneurysm recurrence after coil embolization is common, with reported incidences of up to 33.6 %.[202,266,267,287] Additional coiling of previously embolized and recanalized aneurysms is safe and leads to sufficient occlusion in most aneurysms.[288,289] Furthermore, the risk of additional coil embolization of recurrent cerebral aneurysms does not negate the advantage of the initial embolization and the risks of retreatment may even be smaller than those posed by the initial endovascular aneurysm therapy.[274,290]

There seems, however, to be a small subgroup of patients with wide-necked aneurysm recurrences requiring advanced endovascular therapies and often multiple retreatment sessions. Stent-assisted coil embolization is feasible for the retreatment of these challenging recurrences with wide-necked profile, but an intracranial stent does not by itself guarantee occlusion or stability of the stented aneurysm.[8,291] In a large, prospective multicenter study of 311 patients with 352 retreatment procedures after aneurysm recurrence, it was observed that two of the three treatment-related deaths and the single case of permanent major disability occurred in patients who underwent endovascular treatment more than once for aneurysm recurrence.[290] In another study of 124 recurrent or residual ruptured aneurysms, the risk of rebleeding or regrowth of the aneurysm was associated with large aneurysm size, aneurysm location in the posterior circulation, and aneurysm re-permeabilization.[292]

The results of our study are in agreement with these studies to a large extent. Good clinical outcome and permanent occlusion of the recurrent aneurysm were unlikely in our series if the aneurysm exceeded 2 cm in diameter (P=0.012), if the recurrent diameter of the aneurysm was over 10 mm (P=0.011), or if mass effect was present with a large or giant partially thrombosed aneurysm (P=0.007).

6.4 FLOW-DIVERTING STENTS IN THE TREATMENT OF COMPLEX INTRACRANIAL ANEURYSMS [III]

The initial results published on endoluminal flow-diverting devices (namely the Pipeline embolization device, PED) were exceedingly promising with complete angiographic occlusion in 94 % of the treated aneurysms with angiographic follow-up at 12 months with no major clinical adverse effects periprocedurally or during follow-up.[14] However, an increasing number of perforating branch strokes, stent thromboses, and parent artery stenoses at follow-up were reported in subsequent reports.[17,18,293] The experience in using flow-diverting stents in the treatment of aneurysms of various sizes and shapes is continuously increasing, albeit often only by the method of trial and error, and at times with unacceptable complications. While the initial experience with flow-diverting stents

was mostly limited to the treatment of aneurysms arising from the ICA, reports of flow-diverting stents in the treatment of basilar artery aneurysms, ruptured anterior cerebral artery aneurysms, and even complex middle cerebral artery aneurysms have now been published.[294-296] Although flow-diverting stents are associated with undeniable procedural risks, they represent a true advancement in the endovascular treatment of complex cerebral aneurysms and allow many previously untreatable aneurysms to be successfully managed.

An intracranial stent is considered to be thrombogenic until the stent has been covered by the endothelialisation and the normal intrinsic fibrinolytic activity of the endothelium has renewed. It is, however, still unclear what is the duration of this process with flow-diverting stents, and indeed if it is even possible in the case of multiple overlapping stents with a high metal surface coverage. Our results as well as the reported cases of very late in-stent thrombosis occurring with flow-diverting stents supports the use of prolonged post-procedural antithrombotic therapy which may, on the other hand hinder the goal of the therapy, i.e. occlusion of the stented aneurysm.[297,298] The use of a single flow-diverting stent should be preferred to using multiple overlapping devices since a single stent may provide similar occlusion rates with less complications and better overall outcomes.[250]

As discussed previously with conventional intracranial stents, the timing of the treatment with a flow-diverting stent is of pivotal importance in the treatment of acutely ruptured cerebral aneurysms. Of the four patients who developed periprocedural thromboembolism necessitating administration of intra-arterial abciximab, two had either acute (*N*=1) or subacute (*N*=1) SAH. In addition, the only major complication encountered in the series (fatal ischemic stroke within 24 hours of the procedure) was recorded in a patient with acute SAH. Thereby, either symptomatic or asymptomatic thromboembolic events were encountered in three of the four patients (75 %) treated with a flow-diverting stent during acute or subacute SAH while in the electively treated group thromboembolic events were encountered in only one patient (5 %).

In March 2010, the manufacturer of the Silk flow-diverting stent (Balt Extrusion, Montmorency, France) released an urgent field safety notice advising to use the Silk stent only in adjunct with coil embolization since eight patients treated with a mere Silk stent had died of unexpected aneurysm rupture during short- or mid-term follow-up after the Silk implantation. Thirteen cases of delayed post-procedural aneurysm rupture in twelve different centers were analyzed and it was suggested that intra-aneurysmal thrombus formation after flow-diversion treatment of large and giant cerebral aneurysms may trigger a complex cascade of biologic events and that autolytic effects of the thrombus may lead to delayed rupture of the aneurysm.[16] It is known that many of the observed genetic alterations associated with aneurysm formation also directly affect the repairing processes of the vessel wall (see paragraph 2.1.2). Further knowledge and understanding of the biochemical processes behind aneurysm development and rupture could therefore help also in the patient selection with flow-diverting stents. The release of this urgent safety field notice by the stent manufacturer also reflects the incomplete, yet continuously accumulating clinical knowledge of these novel devices.

Flow-diverting stents offer fascinating opportunities for the treatment of segmentally diseased arteries, often collectively entitled as complex aneurysms. There is, however no formal or universally accepted definition of a ‘complex’ intracranial aneurysm. The following features have been suggested to be commonly associated with complex aneurysms: (1) diameter greater than 25 mm; (2) location of difficult access; (3) presence of previous treatments; (4) absence of collateral circulation; (5) intraluminal thrombus; (6) calcified or otherwise challenging (blister-like, dissecting) aneurysm wall; (7) wide necked or otherwise challenging aneurysm configuration; and (8) parent artery or branches arising directly from the aneurysm.[7,299] Nonetheless, even with the slightly equivocal safety profile of flow-diverting devices, treatment of complex intracranial aneurysms with a flow-diverting stent is justified when conventional endovascular or surgical treatment options are not applicable. Clinical data on flow-diverting stents is difficult to obtain due to rarity

of applicable aneurysms, but larger studies with long-term follow-up and preferably randomized controlled setting are mandatory in evaluating the long-term efficacy and safety of these devices.

6.5 STUDY LIMITATIONS [I-III]

Possibly the most notable limitation of our study is the selection bias. It has been shown that the endovascular treatment decisions vary markedly between centers and individual operators and that the interobserver and intraobserver agreement weakens progressively with increasing response choices (i.e. treatment options).[300,301] The form of treatment for each patient was, however, selected based on a consensus between a neurosurgeon and interventional radiologist who evaluated the data with similar guidelines.

Without systematic post-operative MRI studies it is impossible to know the factual amount of clinically silent microembolic complications associated with different endovascular treatment methods. This is, however, a common phenomenom in this field of science. Since aneurysm formation is a dynamic process, even stable and durable angiographic results may be altered due to *de novo* aneurysm formation. Inherent study limitations arise also from our study population which consists solely of Finnish patients. Since the risk of aneurysm rupture is higher in Finnish and Japanese populations compared to other countries, it may be debatable whether the results of our study can be directly extrapolated to other countries and/or populations.[21,22]

Finally, remarkable inherent study limitations arise from the retrospective setting of this study. The first-generation devices utilized in this study have been replaced by more advanced devices, and it seems evident that these enhanced devices with easier delivery and smaller profile, together with continuously improving microcatheters, guide wires, and image guiding technologies will reduce the clinical applicability of the study results by further improving the technical success rates and by facilitating the treatment of even more peripheral and morphologically challenging aneurysms.

6.6 FUTURE PERSPECTIVES

In the field of interventional neuroradiology the ever increasing pace of technological development is unparalleled, even in the scope of medicine. The continual and rapid advances in material technology and bio-compatible materials, manufacturing processes, biotechnology, and nanotechnology will offer new endovascular treatment options at an accelerating rate, and the role of intracranial stents is becoming ever more important in the management of cerebrovascular diseases. The main focus of aneurysm research and treatment will shift further from reactive treatment of aSAH to aneurysm screening and prevention of aneurysm rupture. Although novel endovascular treatment options may solve some of the challenges involved in the treatment of complex cerebral aneurysms, advanced surgical techniques and endovascular procedures will always be complementary. Only multidisciplinary team approach allows the successful management of previously untreatable cerebral aneurysms – both now and in the future.

7 Conclusions

I Stent-assisted coil embolization is a feasible treatment method for the endovascular treatment of ruptured wide-necked intracranial aneurysms that are difficult to treat with surgical ligation or with balloon-assisted embolization also during acute SAH. The risk of subsequent rerupture of the aneurysm seems to be reduced for aneurysms treated early compared with that of nonsecured aneurysms despite intensified postinterventional antiplatelet therapy, but the optimal antiplatelet medication during acute phase treatment is still equivocal and a longer follow-up series is needed to evaluate the long-term efficacy and safety of stent-assisted coil embolization during acute SAH.

II Stent-assisted coil embolization is beneficial for the treatment of wide-necked recurrent or residual aneurysms. Stability and permanent occlusion of the recurrent aneurysm is however unlikely if the aneurysm exceeds 2 cm in diameter or the largest diameter of the recurrence volume exceeds 10 mm. Alternative treatment methods (i.e. parent vessel occlusion, surgical clipping, or treatment with a flow-diverting device) may also be preferable if mass effect is present with the recurrent aneurysm.

III Many previously untreatable intracranial aneurysms may be successfully treated with a flow-diverting stent, but the associated risk of thromboembolic events is justifiable only if conventional endovascular or surgical treatment options are not applicable. Due to the risk of delayed in-stent thrombosis, meticulous long-term clinical and angiographic follow-up is essential after the deployment of a flow-diverting stent. Perioperative thromboembolic events should be prepared for and treated without unnecessary delays, because they seem to frequently respond to adjunctive medical therapy.

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Olli Tähtinen

Stent-assisted Endovascular Therapy of Complex Intracranial Aneurysms

The incidence of aneurysmal subarachnoid hemorrhage in Finland is among the highest in the world, affecting approximately 1200 patients each year. Endovascular treatment of intracranial aneurysms is firmly established, but endosaccular coil embolization of very wide-necked or otherwise complex cerebral aneurysms is often technically challenging. The development of intracranial stents has revolutionized the endovascular management of complex intracranial aneurysms and many previously untreatable cerebral aneurysms are now within the scope of endovascular treatment. However, many limitations and challenges still persist and the optimal treatment of cerebral aneurysms requires complementary interaction of surgical and endovascular techniques.

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